Non-genetic biomarkers and colorectal cancer risk:

TITLE: Non-genetic biomarkers and colorectal cancer risk: umbrella review and evidence triangulation

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Contributors

ET conceived this study. XZ and DG conducted the literature search. XZ and TY conducted literature screening. XZ extracted the data. YH, GM and DG checked the extracted data. XZ analysed the data and draft the manuscript. All authors interpret the data, revised the manuscript and approved the final version. ET is guarantor.

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Data Availability Statement

No additional data available.

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Novelty & Impact Statements

The identification of specific biomarkers related to CRC risk is essential to understand cancer aetiology and mechanisms of progression. This is the first time that evidence of associations between a wide range of non-genetic biomarkers and colorectal cancer (CRC) risk from a huge number of epidemiological works were evaluated. Three associations detected from meta-analyses of observational studies were classified as suggestive, three and seven associations detected from Mendelian randomisation studies were classified as causality and non-causal respectively.

Abstract

Several associations between non-genetic biomarkers and colorectal cancer (CRC) risk have been detected, but the strength of evidence and the direction of associations are not confirmed. We aimed to evaluate the evidence of these associations and integrate results from different approaches to assess causal inference. We searched Medline and Embase for meta-analyses of observational studies, meta-analyses of randomised clinical trials (RCTs) and Mendelian randomisation (MR) studies measuring the associations between non-genetic biomarkers and CRC risk and meta-analyses of RCTs on supplementary micronutrients. We repeated the meta-analyses using random-effects models and categorised the evidence based on pre-defined criteria. We described each MR study and evaluated their credibility. Seventy-two meta-analyses of observational studies and 18 MR studies on non-genetic biomarkers and six meta-analyses of RCTs on micronutrient intake and CRC risk considering 65, 42 and five unique associations respectively were identified. No meta-analyses of RCTs on blood level biomarkers have been found. None of the associations were classified as convincing or highly suggestive, three were classified as suggestive and 26 were classified as weak. For three biomarkers explored in MR studies, there was evidence of causality and seven were classified as likely non-causal. For the first time, results from both observational and MR studies were integrated by triangulating the evidence for a wide variety of non-genetic biomarkers and CRC risk. At blood level, lower vitamin D, higher homeostatic model assessment-insulin resistance and human papillomavirus infection were associated with higher CRC risk while increased linoleic acid and oleic acid and decreased arachidonic acid were likely causally associated with lower CRC risk. No association was found convincing in both study types.

Introduction

Colorectal cancer (CRC) is the third most common cancer, and the second leading cause of cancer death globally.[1] More than 1.8 million new cases and 881,000 deaths were estimated to have occurred in 2018.[1] Furthermore, although there are stable or descending trends in many high-income countries, their age-specific incidence and mortality rates remain among the highest in the world, especially the incidence among young adults.[2,3]

A biomarker is defined as a cellular, biochemical, or molecular alteration that can be measured and is used to objectively evaluate normal biological or pathological processes.[4] Different types of biomarkers have been investigated in relation to CRC risk. Environmental factors play an important role in the aetiology of CRC through modulating differentiation, apoptosis, angiogenesis, proliferation and immune processes against endothelial cells.[5] Identifying specific biomarkers related to CRC risk is important for understanding cancer aetiology and mechanisms of progression as well as early detection and cancer screening that could consequently reduce CRC mortality. The aims of this review were: (i) to identify meta-analyses of observational studies, meta-analyses of randomised clinical trials (RCTs) and Mendelian randomisation (MR) studies on non-genetic biomarkers and CRC risk; (ii) to evaluate the observed associations and classify the level of credibility of the evidence; and (iii) to integrate the evidence across different approaches using an evidence triangulation framework. Genetic risk factors have been recently explored in a number of field synopses[6,7] and meta-analyses of genome wide association studies,[8,9] and are not considered in this work.

Methods

Search strategy and eligibility criteria

Two reviewers searched Medline and Embase to identify meta-analyses of observational studies (01 Jan 2010 to 14 Jun 2019), meta-analyses of RCTs (01 Jan 2010 to 14 Jun 2019) and MR studies (up to 20 Jun 2019) investigating the association between non-genetic biomarkers and CRC risk. As no meta-analyses of RCTs on biomarkers were identified, we included meta-analyses of RCTs

(01 Jan 2010 to 14 Jun 2019) on micronutrient intake as proxies of micronutrient blood levels. Systematic reviews without meta-analyses were excluded. Meta-analyses of observational studies on non-genetic biomarkers and CRC risk published before 2010 had been previously reviewed in a published umbrella review.[10] The main results of these studies were extracted from the published umbrella review and were further evaluated and assessed together with additional studies published from 2010 onwards. A parallel review was conducted by a third reviewer. In the case of any discrepancy in assessments, a final decision was made after discussion. The details of all search strategies are provided in Supplementary Table 1. We first reviewed the title and abstract of the identified studies and then evaluated the full text of all potential eligible studies. We manually checked the references of all retrieved articles to include any missed relevant studies. Studies investigating the associations between genetic or non-genetic biomarkers and CRC screening, diagnosis, survival and prognosis were excluded.

Data extraction

One investigator extracted information from each eligible study and two other investigators checked the extracted data. A fourth investigator was involved to judge any discrepancies. For meta-analyses of observational studies, we extracted the first author, year of publication, number of studies considered, epidemiological study design, biomarker details, outcome and study population. We also recorded the study specific relative risk estimates (risk ratio, odds ratio, hazard ratio, standard mean difference, weighted mean difference, standardized correlation coefficient), details of the applied statistical models, correspondent confidence intervals and number of cases and participants. For meta-analyses of RCTs on micronutrient intake, we further extracted the dose and duration of supplementation, number of events and type of intervention in the control group. For MR studies, we extracted: the exposure, study design, effect estimate unit, sample size, population ethnicity for both exposure and outcome groups, main MR estimate and any sensitivity analyses for the associations of genetic instruments with the exposure and outcome, total variance level

explained by the genetic instrument assuming an additive model (R^2), and the approximate statistical power (where presented).

Statistical analysis

For the meta-analyses of observational studies, we re-estimated the summary effect size and its confidence interval. As the most commonly used DerSimonian and Laird (DL) estimator tends to underestimate the 95% CI when less than 10 studies are included,[11] we used the Hartung-Knapp-Sidik-Jonkman (HKSJ) method as the main random effect estimator.[12] The HKSJ estimator consistently results in more adequate error rates even when the number of studies is small or between studies heterogeneity exists.[12,13] The meta-analysis P value threshold was set at 0.05. The Paule-Mandel (PM) estimator could give an accurate result when between study heterogeneity is large but the number of studies is not small.[13] Therefore, DL[14] and PM[15] methods were also applied as sensitivity analyses. We quantified the heterogeneity of each meta-analysis by calculating the I^2 value and its 95% prediction interval.[16,17] We used the Egger regression asymmetry test to estimate any small study effect.[18] The excess significance test was performed to evaluate whether the observed number of studies with positive results was significantly greater than the expected number by using a chi square test.[19] For both the small study effect and the excess significance test we used $P<0.1$ as the threshold.

Stata version 14.0 and "metafor" package[20] in R 3.5.1 were used for statistical analysis. Two-tailed P values were used.

Credibility Assessment

If there were more than one meta-analysis of observational studies or more than one MR study investigating the association between the same biomarker and CRC risk, we compared the direction, level of statistical significance ($P\leq0.05$) and effect size. The most recent meta-analysis with the largest number of prospective studies was retained for further analysis. The most recent MR

study (unless a previous MR study employed a stronger genetic instrument and/ or had a larger sample size at the outcome arm) was retained for further comparison.

If we identified meta-analyses of observational studies and MR studies investigating the same biomarker, we compared the direction and level of statistical significance (P≤0.05). All associations explored in meta-analyses of observational studies and/ or MR studies are presented in an evidence triangulation plot.[21,22]

We categorised the evidence from meta-analyses of observational studies for each eligible biomarker in four categories according to previously defined criteria that considered the quantified evidence, statistical significance, heterogeneity, small study effect, excess significance bias and prediction interval (convincing or class I, highly suggestive or class II, suggestive or class III, weak or class IV and no association).[23,24] The evidence classification criteria are described in Table 1. For each convincing or highly suggestive association, we re-checked the eligibility for each individual study, re-evaluated the accuracy of extracted data and reassessed the evidence after restricting the analysis to prospective cohort studies.

Associations detected from MR studies were categorized into 'Evidence of causality', 'Likely non-causal' and 'Unknown' by considering statistical significance (p<0.05), pre-estimated power (Power≥0.8 regarded as sufficient) and evidence of bias due to directional pleiotropy (Table 1).

Results

The literature search returned 9227 hits for the meta-analyses of observational studies and RCTs, and returned 75 hits for MR studies. After applying the pre-defined inclusion and exclusion criteria, 72 meta-analyses of observational studies, 18 MR studies and six meta-analyses of RCTs on supplementary micronutrients were identified (Figure 1).

Meta-analyses of observational studies

A total of 145 effect estimates for 65 unique biomarkers were extracted from the 72 included meta-analyses of observational studies (Supplementary Table 4). The median number of included component studies for each meta-analysis was 7 (range: 2 – 31). The median number of cases was 1,170 (range: 37 – 62,814) and of participants was 4,240 (range: 76 – 7,725,310). More than one meta-analysis of observational studies was identified for 20 biomarkers (Supplementary Table 6): helicobacter pylori infection (H. pylori, n=9), human papillomavirus infection (HPV, n=8), blood levels of folate (n=6), blood levels of vitamin B12 (n=5), blood levels of vitamin B6 (n=5), blood levels of vitamin B2 (n=2), blood levels of 25-hydroxyvitamin D (n=10), C-reactive protein (CRP, n=3), interleukin-6 (IL-6, n=2), fasting glucose (n=6), C peptide (n=3), IGF-1 (n=3), IGF-2 (n=2), insulin-like growth factor-binding protein 3 (IGFBP-3, n=2), triglycerides (n=3), high-density lipoprotein cholesterol (HDL-cholesterol, n=2), adiponectin (n=7), leptin (n=4), telomere length (n=3) and homocysteine (n=3). Seventeen out of the 20 (85%) overlapping meta-analyses agreed on the direction of the effect estimate, 12 of these 17 agreed on the level of statistical significance and 10 of these 12 associations were statistically significant (Supplementary Table 6).

After removing the overlapping meta-analyses, a total of 65 unique biomarkers were retained for further statistical analysis (Figure 3, and Supplementary Table 2 & 7). We categorized the biomarkers into seven categories: fatty acid/lipid metabolism biomarkers (n=14), micronutrients (n=10), infectious agents (n=13), inflammatory markers (n=2), insulin related biomarkers (n=10), protein/amino acids (n=10) and other biomarkers (n=6).

A total of 29 associations among the 65 non-overlapping meta-analyses of observational studies (45%) were statistically significant ($P<0.05$) by using the HKSJ meta-analysis estimator (Supplementary Table 2, Figure 2). Sensitivity analyses using the DL and PM estimator are presented in Supplementary Table 7. Eight and five associations were upgraded when using DL estimator or the PM estimator instead of the HKSJ estimator respectively. Sixteen out of the 29 significant biomarkers

were associated with increased CRC risk. In these 29 statistically significant associations, 7 (24%) had P<0.001, 24 (83%) had a 95% prediction interval that excluded null, 14 (48%) had more than 1,000 cases, 13 (45%) had no obvious large heterogeneity (I^2<50%), 20 (69%) were not subject to small-study effect or excess significance bias (Supplementary Table 2). After applying the credibility criteria, one biomarker (fasting glucose [RR (95% CI): 1.27 (1.11, 1.45)]) was classified as highly suggestive and three biomarkers were classified as suggestive (homeostatic model assessment-insulin resistance [HOMA-IR; RR (95% CI): 1.56(1.22, 1.98)], 25-hydroxyvitamin D [RR (95% CI): 0.67(0.54, 0.83)] and HPV [RR (95% CI): 3.52(1.77, 7.00)]). For the associations classified as 'highly suggestive', we checked the eligibility of each component study, evaluated the accuracy of the extracted data and reassessed the evidence after restricting the analysis to only including prospective studies. The evidence of association between fasting glucose and CRC risk was downgraded to 'weak'.

We identified six meta-analyses of RCTs on associations between supplementary micronutrients and CRC risk, but none of them reported a statistically significant association (Supplementary Table 8).

Mendelian randomisation studies

Sixty-six MR studies were extracted from 18 publications (Supplementary Table 5). The median number of cases for the outcome arm of each included MR study was 13,012 (range: 329-30,480), the median number of participants was 36,137 (range: 727-382,756) and the median variance explained by each genetic instrument was 2.92% (range: 0.3-60.4%). Eight (12%) MR studies had enough power (≥0.8) to detect a statistically significant effect estimate. Overlapping MR studies were detected for 14 biomarkers (Supplementary Table 6). Nine of the 14 MR studies agreed on the direction of the effect size and eight of which agreed on the level of statistical significance: overlapping MR studies for plasma arachidonic acid (n=2) and plasma linoleic acid (n=2) agreed on the direction of effect size and the effect size estimates were statistically significant; overlapping MR

studies for adiponectin (n=3), fetuin-A (n=2), docosapentaenoic acid (DPA, n=2), DHA (n=2), low-density lipoprotein cholesterol (LDL-cholesterol, n=3) and telomere length (n=2) were concordant in the direction but the effect size estimates were not statistically significant; overlapping MR studies for total cholesterol (n=2) agreed on the direction but not on the level of statistical significance; MR studies for blood levels of 25-hydroxyvitamin D (n=8), EPA (n=2), triglyceride (n=3), HDL-cholesterol (n=3) and CRP (n=3) neither agreed on direction nor on statistical significance.

The biomarkers of the 66 MR analyses were categorized into six categories: micronutrients (n=17), fatty acid/lipid metabolism biomarkers (n=30), inflammatory markers (n=4), protein/amino acid (n=9), insulin related markers (n=4) and other biomarkers (n=2) (Supplementary Table 5). Nine (14%) biomarkers (stearic acid, arachidonic acid [n=2], linoleic acid [n=2], oleic acid, palmitoleic acid, total cholesterol and CRP) reported statistically significant associations (at $P<0.05$ or at a study specified threshold due to multiple testing). After removing the overlapping MR studies, 42 biomarkers were retained for analysis (Supplementary Table 3, Figure 3), three biomarkers (arachidonic acid [OR (95% CI): 1.05(1.03, 1.07)], linoleic acid [OR (95% CI): 0.95(0.93, 0.97)] and oleic acid [OR (95% CI): 0.77(0.65, 0.92)]) with statistically significant effect estimates and without evidence of biological pleiotropy were classified as having 'Evidence of causality'. Seven MR studies were categorised as 'Likely non-causal', since these studies had enough statistical power and no evidence of biological pleiotropy, but they were statistically non-significant (LDL–cholesterol, omega-6 polyunsaturated fatty acids, total cholesterol, selenium, vitamin B12, telomere length, adiponectin).

Twenty non-genetic biomarkers were analysed in both meta-analyses of observational studies and MR studies (Supplementary Table 6, Figure 2). Ten of the 20 biomarkers (25-hydroxyvitamin D, selenium, vitamin E, total cholesterol, LDL-cholesterol, CRP, fasting glucose, glycated haemoglobin [HbA1C], adiponectin, telomere length) agreed on the direction of the effect size, six (selenium, vitamin E, total cholesterol, LDL-cholesterol, HbA1C, telomere length) of which

agreed on the level of statistical significance (not significant). One biomarker (25-hydroxyvitamin D) was analysed by three different study types (meta-analysis of observational study, MR studies and meta-analysis of RCTs on supplementary vitamin D), but only the meta-analyses of observational studies reported a statistically significant association.

Discussion

In this study, a comprehensive overview of associations between a wide range of non-genetic biomarkers and CRC risk was conducted by triangulating evidence from meta-analyses of observational studies, MR studies and meta-analyses of RCTs. The non-genetic biomarkers for CRC risk which were studied covered 7 categories and CRC risk was associated with 34 examined biomarkers. There is a gap of meta-analyses of RCTs or even individual RCTs on biomarkers of CRC risk and these were only examined in observational studies. We, therefore, included meta-analyses of RCTs of supplementary micronutrients as proxies.

Meta-analyses of observational studies

Twenty-nine biomarkers were associated with CRC risk at $p<0.05$ from meta-analyses of observational studies, but none of these association was classified as convincing or highly suggestive. Of these 29 statistically significant associations, three (25-hydroxyvitamin D, HPV and HOMA-IR [HOMA-IR=glucose × insulin/405]) were classified as suggestive and 26 as weak.

The association between vitamin D concentration and CRC risk was classified as suggestive (Class III) and indicated that a higher blood concentration of vitamin D was associated with a 33% decrease in CRC risk. This result was consistent among all eight overlapping meta-analyses. Experimental studies based on mouse models have indicated that the potent steroid hormone Calcitriol (the active form of vitamin D) may play a protective role against CRC through the regulation of proliferation, pro-differentiation, pro-apoptosis, anti-angiogenesis and immune modulation.[25] However, results from RCTs do not support a causal role between supplementary vitamin D (from 800IU/day to 1000 IU/day with or without calcium supplementation for 1 to 7 years) and CRC risk (Supplementary Table 8). Similarly, the eight overlapping MR studies included in this review did not identify a causal association between blood level of vitamin D and CRC risk (Supplementary Table 6). Therefore, currently, there is no evidence for a clear causal role of vitamin D on CRC risk. It is also possible that the non-significant results from RCTs and MR studies are due to the distinct limitations

of these two study designs, such as limited follow-up time, insufficient supplementary dose and contamination of controls for RCTs and collider bias, limited power and potential pleiotropy for MR studies.

A statistically significant association between diabetes and CRC risk has been previously identified by an umbrella review published in 2014.[26] In the current study, among the insulin related biomarkers, HOMA-IR (a method to quantify insulin resistance based on the blood concentration of glucose and insulin) showed suggestive evidence (Class III) for an association with a higher risk of CRC. Similarly, IGF-1 and fasting glucose had weak evidence for an association with CRC risk. Elevated glucose and insulin levels may increase CRC risk through their pro-proliferation, pro-angiogenesis and apoptosis inhabitation effects against tumour cell.[27] For example, exposure to high glucose could lead to increased generation of reactive oxygen intermediates and subsequently could induce apoptosis of endothelial cells.[28] In addition, hyperglycaemia could increase the concentration of circulating inflammatory cytokines leading to chronic inflammation, which has been suggested to relate to tumour generation.[29,30] However, in this review, we did not find evidence of an association between inflammatory markers and CRC risk. The tumour cell growth simulated by high concentrations of insulin through the activation of IGF-1, and the possible protective effect of the use of metformin (found in a meta-analysis including 12 cohort studies, seven case-controls studies and one RCT)[31] on CRC development further supports the insulin-CRC association. In conclusion, preclinical and epidemiological evidence supports an association between insulin related biomarkers on CRC risk, but causality is not supported by MR studies. We should note that diabetes shares many risk factors with CRC, which could explain the observed associations from observational studies.

Interestingly, seven different types of pathogenic micro-organisms were found to be related to CRC risk, but most of the evidence was classified as weak due to small number of cases. Only HPV showed a suggestive association with CRC risk. HPV is a non-enveloped double stranded DNA virus with more than 170 types. Twelve of these types are considered as causal risk factors for cervical

cancer (known as high-risk HPV types) by IARC Monographs.[32,33] In addition, HPV 16, HPV 18 and HPV 33 have commonly been found in CRC cases.[34,35] The potential mechanisms of HPV on colorectal carcinogenesis include viral integration in host cells and expression of E6 and E7 oncoproteins, however, evidences of whether HPV infection is truly involved in colorectal carcinogenesis is still not convincing.[36] Furthermore, this finding should be interpreted with caution, since the HPV-CRC association was analysed without stratifying by HPV type. Meanwhile, all the included meta-analyses synthesised retrospective observational studies, therefore the observed associations could be due to reverse causality.

Overall, meta-analyses of observational studies indicated weak associations between non-genetic biomarkers and CRC risk. In this review, only seven out of 65 associations fulfilled the P-value threshold of convincing evidence, and of these three were based on evidence from less than 1000 cases, three did not have a statistically significant p-value for their largest individual study and for one there was evidence of small study effect bias and excess significance bias. Despite weak evidence after applying the pre-defined credibility criteria, we cannot ignore the clinical importance of these associations. Notably, most (85%) of the overlapping studies agreed on the direction of effect estimate and over half (60%) agreed on both the direction and statistical significance.

Mendelian randomisation studies

Almost half of the biomarkers identified from MR studies were biomarkers of fatty acid / lipid metabolism. Most of the detected MR studies had insufficient power (<0.8). There were nine MR studies that reported statistically significant results. After retaining the largest MR study for each biomarker and applying the pre-defined assessment criteria, we found evidence that high blood levels of linoleic acid and oleic acid and low blood levels of arachidonic acid were associated with low CRC risk. Conversely, LDL–cholesterol, omega-6 polyunsaturated fatty acids (n-6 PUFAs), total cholesterol, selenium, vitamin B12, telomere length and adiponectin were not found to be associated with CRC risk.

n-3 and n-6 PUFAs are essential fatty acids and cannot be produced in the human body.[37 38] The beneficial effects of high levels of n-3 PUFAs and low levels of n-6 PUFAs on CRC risk reduction remain debatable. In this review, a weak protective effect of n-3 PUFAs on CRC risk was detected from meta-analyses of prospective observational studies while MR analyses did not show any evidence of causality. Similarly, RCTs did not report any association between supplementation of n-3 fatty acids (combination of EPA and DHA) and CRC incidence.[39,40] Arachidonic acid is an n-6 PUFA, which in this review is suggested to causally increase the risk of CRC. The potential mechanism is that arachidonic acid can regulate CRC development through the inhibition of cyclooxygenase (COX)/lipoxygenase (LOX) and has a competitive relation to DPA in terms of COX enzyme activity.[37,41] Oleic acid and linoleic acid are two of the main components of olive oil and have been examined as protective biomarkers for CRC risk by MR studies in this review. These findings, along with evidence from a literature review on olive oil intake and a cohort study on Mediterranean diet,[42,43] support the beneficial effect of oleic acid and linoleic acid on CRC risk. However, the genetic instruments for the two n-6 PUFAs are similar, which indicates the possibility that arachidonic acid and linoleic acid may share the same pathway to influence CRC risk and represent vertical pleiotropy.

Overall, we found that there was either lack of evidence or that the credibility of evidence varied across the three different study designs. For instance, evidence detected from meta-analyses of observational studies was not confirmed by MR studies or meta-analyses of RCTs on supplementary micronutrients (i.e. in vitamin D). This may be either due to differences in the study designs (observational study tests the presence of associations while MR study and RCT explore causality) or due to their inherent distinct limitations and biases. Conversely, four 'likely non-causal' associations identified from MR studies also were reported as negative results by meta-analyses of observational studies, i.e. selenium, total cholesterol, LDL–cholesterol and telomere length.

Strengths and limitations

This umbrella review presents for the first time, integrated evidence from meta-analyses of observational studies, MR studies and RCTs with the aim to improve our understanding of the associations between non-genetic biomarkers and CRC risk. Each of the included studies have different strength and limitations and, if consistent, could strengthen our confidence in findings.[44] The umbrella review design has a number of strengths as previously summarised.[45-48] It also has several limitations. First, in an umbrella review, only systematic reviews with meta-analyses and MR studies are included, thus associations with biomarkers that have not been included in meta-analyses are not evaluated (i.e. circulation sex hormone levels).[49,50] We did not search for pre-print articles which are not peer reviewed, and we have therefore not included studies of newly detected CRC related biomarkers. Given that no meta-analyses of RCTs on biomarkers were identified, we included meta-analyses of RCTs on intake of micronutrients as proxies of micronutrient levels measured in blood. Along with the inclusion of MR studies, these might offset the absence of meta-analyses of RCTs. A note of caution though is the uncertain association between supplementary dose and physiological dose of micronutrients across participants. Second, there might have been heterogeneity of effects based on anatomical site,[51] gender, body mass index, diabetes mellitus and other risk factors,[52] but we did not perform any subgroup analysis. Third, we did not evaluate the quality assessment of the component studies of each meta-analysis of observational studies (apart from meta-analyses classified as convincing or highly suggestive) and the eligibility of component studies depended on the authors of each meta-analysis. Most of the included meta-analyses estimated the quality of the individual studies by applying the Newcastle-Ottawa Scale, which has low reliability between independent reviewers.[53] Fourth, the limitations of the adopted credibility assessment criteria have been described previously and also apply here.[45-48] Finally, evidence from meta-analyses of observational studies could be biased by confounding factors or by reverse causality.

Conclusion

This umbrella review represents a comprehensive summary and evidence triangulation of a wide range of CRC risk associated non-genetic biomarkers. In conclusion, we report and classify the evidence for non-genetic biomarkers detected from meta-analyses of observational studies, MR studies and meta-analyses of RCTs. Convincing evidence of a clear role of a non-genetic biomarker in CRC risk has not been detected from meta-analyses of observational studies. From MR studies, a likely causal increased CRC risk with arachidonic acid and a likely causal decreased risk with linoleic acid and oleic acid were suggested. Conversely, seven biomarkers (LDL–cholesterol, n-6 PUFAs, total cholesterol, selenium, vitamin B12, telomere length and adiponectin) are likely non-causal. Four (LDL–cholesterol, total cholesterol, selenium and telomere length) of these seven biomarkers have consistent results (likely non-causal) from MR and meta-analyses of observational studies.

Conflict of interest

None declared.

Ethical approval

Not required.

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Tables

Table 1 Credibility Assessment Criteria for Meta-analyses of Observational Studies and Mendelian randomisation study	
Evidence category	Criteria
Meta-analyses of observational studies	
Convincing (class I)	P < 0.001; >1000 cases; P < 0.05 in the largest study. A 95% PI that excluded the null; I^2 <50%. No evidence of small-study effect (P > 0.10); and no excess significance bias (P > 0.10).
Highly suggestive (class II)	P < 0.001; >1000 cases. P < 0.05 in the largest study;
Suggestive (class III)	P < 0.001; >1000 cases
Weak (class IV)	P < 0.05
No association	P ≥ 0.05
Mendelian randomisation study	
Evidence of causality	P<0.05 or threshold set up by individual study due to multiple testing; evaluated pleiotropy but have no evidence of directional pleiotropy.
Likely non-causal	P>0.05 or threshold set up by individual study due to multiple testing; Power≥0.8; Consistent evidence between main MR analysis and sensitivity analyses; Evaluated pleiotropy but have no evidence of directional pleiotropy.
Unknown	Studies that cannot be classified as either 'Evidence of causality' or 'Likely non-causal'.
PI: prediction interval	

Figure legends

Figure 1A: PRISMA flow diagram illustrating the study screening and selection process for meta-analyses of observational studies and meta-analyses of randomised clinical trials (performed on 14/06/2019)

Figure 1B: PRISMA flow diagram illustrating the study screening and selection process for Mendelian randomisation studies (performed on 20/06/2019)

Figure 2 Evidence triangulation bubble plot for biomarkers detected from meta-analyses of observational studies and MR studies

The bubble size of meta-analyses of observational studies represents the number of cases and the bubble size of MR studies represents the number of CRC cases divided by 5. MR only: Biomarkers only detected in MR studies, MA only: Biomarkers only detected in meta-analyses of observational studies, LA: Linoleic acid, AA: Arachidonic acid, V-B12/B6/D/E/A: Vitamin B12/B6/D/E/A, Adiponectin1: Adiponectin in European and United State population, Adiponectin2: Adiponectin in European population only, TC: Total cholesterol, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, TL: Telomere length, n-6 PUFA: n-6 polyunsaturated fatty acid, IGF-1/2: Insulin-like growth factor 1/2, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, DPA: Docosapentaenoic acid, CRP: C-reactive protein, IL-6: Interleukin 6, HbA1C: glycated hemoglobin, GDF-15: Growth differentiation factor 15, IGE: Serum immunoglobulin E, ALA: α-Linolenic acid, DGLA: Dihomo-γ-linolenic acid, MUFA: Mono-unsaturated fatty acids, Blood-A/B/AB/O: Blood group A/B/AB/O, F-glucose: Fasting glucose, F-insulin: Fasting insulin, HPV: Human papillomavirus, n-3 PUFA: long chain n-3 polyunsaturated fatty acid, HOMA-IR: homeostatic model assessment-insulin resistance, MMP7: Matrix metalloproteinase-7, S-bovis: Streptococcus bovis, IGFBP 1/2/3: Insulin-like growth factor-binding protein 1/2/3, CD26: Dipeptidyl peptidase IV, S-bovis-faeces: Streptococcus bovis in faeces, H.pylori: Helicobacter pylori, B.b: Bifidobacterium, E.b: Enterobacteriaceae, HCI: Human cytomegalovirus infection, F.n: F. nucleatum, Hcy: Homocysteine, TB: Total bacteria, F.b: Faecalibacterium prausnitzii, E.c: Escherichia coli, L.b: Lactobacillus, F-proinsulin: fasting proinsulin

Figure 3A Forest plot for evidence of associations between non-genetic biomarkers and CRC risk from meta-analyses of observational studies (metric: odds ratio and risk ratio)

Figure 3B Forest plot for evidence of associations between non-genetic biomarkers and CRC risk from meta-analyses of observational studies (metric: standardized mean difference)

Figure 3C Forest plot for evidence of associations between non-genetic biomarkers and CRC risk from MR studies (metric: odds ratio)

CRC: colorectal cancer, CI: confidence interval, results of meta-analyses were analysed by using Hartung-Knapp-Sidik-Jonkman method, RR: risk ratio, SMD: standard mean difference, OR: odds ratio, LC n-3 PUFA: long chain n-3 polyunsaturated fatty acid, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, DPA: Docosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, HPV: Human papillomavirus, H.pylori: Helicobacter pylori, CRP: C-reactive protein, IL-6: Interleukin 6, HOMA-IR: homeostatic model assessment-insulin resistance, IGF 1/2: Insulin-like growth factor 1/2, IGFBP 1/2/3: Insulin-like growth factor-binding protein 1/2/3, HbA1c: glycated hemoglobin, MMP7: matrix metalloproteinase-7, CD26: dipeptidyl peptidase IV, *: total number of participants for exposure and CRC Genome-wide association studies, SNP: Single Nucleotide Polymorphism, GRS: genetic risk

score, AA: arachidonic acid, DGLA: dihomo-γ-linolenic acid, LA: linoleic acid, ALA: α-Linolenic acid, GDF-15: Growth differentiation factor 15.

Supplementary tables

Supplementary Table 1 Search strategy

Search strategy for meta-analyses of observational studies and randomised clinical trials

	MEDLINE		EMBASE
1	((rectal or rectum or colonic or colon or colorectal or bowel* or sigmoid or intestin*) adj3 (cancer* or carcinoma* or neoplas* or tumor* or tumour* or adenocarcinoma* or adeno?carcinoma* or adenom* or lesion* or CRC)).mp.	1	((rectal or rectum or colonic or colon or colorectal or bowel* or sigmoid or intestin*) adj3 (cancer* or carcinoma* or neoplas* or tumor* or tumour* or adenocarcinoma* or adeno?carcinoma* or adenom* or lesion* or CRC)).mp.
2	exp Colorectal Neoplasms/	2	exp colon tumor/
3	1 or 2	3	exp rectum tumor/
4	meta analy$.tw.	4	exp colon carcinoma/
5	metaanaly$.tw.	5	exp colorectal carcinoma/
6	(systematic adj (review$1 or overview$1)).tw.	6	exp rectum carcinoma/
7	Meta-Analysis/	7	exp colon cancer/
8	exp "REVIEW LITERATURE AS TOPIC"/	8	exp rectum cancer/
9	exp Meta-Analysis as Topic/	9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	4 or 5 or 6 or 7 or 8 or 9	10	(meta adj analy$).tw.
11	3 and 10	11	metaanalys$.tw.
12	limit 11 to yr="2010 - 2019"	12	(systematic adj (review$1 or overview$1)).tw.
		13	meta analysis/
		14	exp "systematic review"/
		15	exp "meta analysis (topic)"/
		16	10 or 11 or 12 or 13 or 14 or 15
		17	9 and 16
		18	limit 17 to yr="2010 - 2019"

Search strategy for Mendelian randomisation studies

((rectal or rectum or colonic or colon or colorectal or bowel* or sigmoid or intestin*) and (cancer or carcinoma* or neoplas* or tumor or tumour or adenocarcinoma* or adeno?carcinoma* or adenom* or lesion* or CRC) and (Mendelian and randomi*)).mp.

Supplementary Table 2 Characteristics and main findings of meta-analyses of observational studies reporting unique non-genetic biomarkers and CRC risk (HKSJ estimator)

First author, Year (Citation)	Biomarker	Comparison	No of studies	No of cases	Total No	Metric	Effect size (95% CI)	P value	I^2	$^1P_{Egger}$	95% Prediction interval	$^2P_{sig}$	Evidence
Fatty acid/Lipid metabolism biomarkers													
Yang B,2014	LC n-3 PUFA	Highest vs. lowest categories	3	421	1,826	RR	0.58(0.40, 0.84)	0.0042	0.21%	0.78	0.578(0.398, 0.841)	NA	Weak
Yang B,2014	Biospecimen EPA 20:5 (n-3)	Highest vs lowest categories	4	421	1,826	RR	0.64(0.42, 0.96)	0.0314	9.24%	0.50	0.637(0.422, 0.961)	NA	Weak
Yang B,2014	Biospecimen DHA 22:6 (n-3)	Highest vs. lowest categories	4	421	1,826	RR	0.51(0.28, 0.93)	0.0266	46.59%	0.19	0.513(0.284, 0.925)	NA	Weak
Yang B,2014	Biospecimen DPA 22:5 (n-3)	Highest vs. lowest categories	3	243	1,366	RR	0.56(0.29, 1.07)	0.0788	37.89%	0.46	0.561(0.295, 1.069)	NA	No
Yang B,2014	Blood EPA 20:5 (n-3)	Mean (% total fatty acids)	5	195	384	SMD	-0.98(-2.87, 0.91)	0.308	98.87%	0.01	-0.983(-2.873, 0.907)	NA	No
Yang B,2014	Blood DHA 22:6 (n-3)	Mean (% total fatty acids)	5	195	384	SMD	-0.07(-0.31, 0.17)	0.5718	35.10%	0.41	-0.068(-0.306, 0.169)	NA	No
Yang B,2014	Blood DPA 22:5 (n-3)	Mean (% total fatty acids)	5	195	384	SMD	0.43(-0.27, 1.12)	0.2292	92.11%	0.00	0.427(-0.269, 1.122)	NA	No
Yang B,2014	Adipose EPA 20:5 (n-3)	Mean (% total fatty acids)	2	93	204	SMD	0.07(-0.21, 0.36)	0.6083	3.39%	/	0.074(-0.208, 0.356)	0.75	No
Yang B,2014	Adipose DHA 22:6 (n-3)	Mean (% total fatty acids)	2	93	204	SMD	-0.02(-0.37, 0.32)	0.8999	35.64%	/	-0.022(-0.368, 0.324)	NA	No
Yang B,2014	Adipose DPA 22:5 (n-3)	Mean (% total fatty acids)	2	93	204	SMD	0.12(-0.16, 0.39)	0.4082	0.07%	/	0.117(-0.160, 0.395)	0.69	No
Yao X, 2015	HDL-cholesterol	Highest vs. lowest categories	12	2,542	136,698	RR	0.83(0.67, 1.04)	0.1043	53.08%	0.39	0.83(0.67, 1.04)	0.01	No
Yao X, 2015	LDL-cholesterol	Highest vs. lowest categories	5	1,626	9,175	RR	1.04 (0.57, 1.92)	0.8908	85.67%	0.16	1.04(0.57, 1.92)	0.0002	No
Yao X, 2015	Total cholesterol	Highest vs. lowest categories	28	10,892	7,725,310	RR	1.11(0.98, 1.27)	0.1043	76.10%	0.60	1.12(0.98, 1.27)	NA	No
Yao X, 2015	Triglyceride	Highest vs. lowest categories	19	8,127	2,252,217	RR	1.17 (0.99, 1.37)	0.0598	47.77%	0.22	1.17(0.99, 1.37)	NA	No
Infectious agents													
Ibragimova MK,2018[25]	HPV	CRC tissue vs Cancer-free tissue	17	1,722	2,468	RR	3.52(1.77, 7.00)	0.0003	75.66%	0.6453	3.52(1.77, 7.00)	NA	Suggestive
Bai B,2016	Human cytomegalovirus infection	Tumour tissue vs normal tissue	4	480	960	OR	6.47(4.23, 9.89)	6.7839E-18	13.74%	0.70	6.47(4.23, 9.89)	0.99	Weak
Boleij A,2011	Streptococcus bovis	CRC in S.bovis type 1 & type 2	6	189	340	OR	9.44(4.43, 20.11)	5.95E-09	18.72%	0.57	9.44(4.43, 20.11)	NA	Weak

Liu C,2016	H.pylori	CRC vs non-CRC	20	3,228	4,377	OR	1.38(1.01, 1.89)	4.00E-02	82.00%	0.90	1.38(1.02, 1.89)	0.27	Weak
Repass J,2018	F. nucleatum	CRC tissue vs adjacent normal tissue	2	139	278	r	0.40(0.16, 0.63)	0.00100	40.05%	/	0.38(0.16, 0.56)	NA	Weak
Liu H,2016	Enterobacteriaceae	Healthy controls (logarithmic number of bacteria per gram stool)	2	37	76	SMD	2.62(0.62, 4.61)	0.0101	87.87%	/	2.62(0.62, 4.61)	NA	Weak
Liu H,2016	Bifidobacterium	Healthy controls (logarithmic number of bacteria per gram stool)	4	127	315	SMD	-3.24(-6.32, -0.16)	0.039	98.08%	0.07	-3.24(-6.32, -0.16)	0.00	Weak
Liu H,2016	Faecalibacterium prausnitzii	Healthy controls (logarithmic number of bacteria per gram stool)	3	86	233	SMD	-0.31(-0.69, 0.06)	0.1	25.76%	0.60	-0.31(-0.69, 0.06)	0.80	No
Liu H,2016	Total bacteria	Healthy controls (logarithmic number of bacteria per gram stool)	3	86	233	SMD	0.29(-0.74, 1.31)	0.5825	87.31%	0.07	0.29(-0.74, 1.31)	0.28	No
Krishnan S,2014	Streptococcus bovis in faeces	CRC vs non-CRC	3	148	414	OR	3.10(0.68, 14.20)	0.1456	56.37%	0.23	3.10(0.68, 14.20)	NA	No
Liu H,2016	Lactobacillus	Healthy controls (logarithmic number of bacteria per gram stool)	4	127	315	SMD	-1.85(-5.33, 1.64)	0.2993	99.15%	0.19	-1.85(-5.33, 1.64)	0.00	No
Liu H,2016	Bacteroides-Prevotella group	Healthy controls (logarithmic number of bacteria per gram stool)	3	97	255	SMD	-0.70(-2.33, 0.94)	0.403	95.30%	0.83	-0.70(-2.33, 0.94)	NA	No
Liu H,2016	Escherichia coli	Healthy controls (logarithmic number of bacteria per gram stool)	2	90	239	SMD	1.38(-1.34, 4.10)	0.3195	97.96%	/	1.38(-1.34, 4.10)	0.00	No
Inflammatory Markers													
Zhou B,2014	CRP	1-unit change in ln (mg/l)	18	4,779	152,942	RR	1.14(1.04, 1.25)	0.0059	72.80%	0.05	1.14(1.04, 1.25)	0.03	Weak
Zhou B,2014	IL-6	1-unit change in ln (mg/l)	6	1,125	9,909	RR	1.09(0.85, 1.39)	0.4959	47.99%	0.19	1.09(0.85, 1.39)	0.595	No
Insulin related biomarkers													

Xu J,2016	Fasting glucose	Highest vs lowest categories (mmol/L)	26	20,390	5,105,567	RR	1.27(1.11, 1.45)	0.0006	66.17%	0.0106	1.27(1.11, 1.45)	NA	Highly suggestive
Xu J,2016	HOMA-IR	Highest vs lowest categories (fasting glucose (mmol/L) × fasting insulin (mIU/L) / 22.5)	9	2,956	18,358	RR	1.56(1.22, 1.98)	0.0003	38.91%	0.18	1.56(1.22, 1.99)	NA	Suggestive
Xu J,2016	Fasting insulin	Highest vs lowest categories (mIU/L)	11	3,191	26,301	OR	1.40 (1.12, 1.74)	0.0031	24.65%	0.86	1.40(1.12, 1.74)	NA	Weak
Chi F,2013	IGF 1	Highest with lowest categories	17	3,807	11,613	OR	1.31(1.05, 1.63)	0.0187	48.42%	0.28	1.31(1.05, 1.63)	NA	Weak
Chi F,2013	IGF 2	Highest with lowest categories	6	783	4,007	OR	1.52(0.99, 2.34)	0.0549	42.30%	0.62	1.52 (0.99, 2.34)	NA	No
Chi F,2013	IGFBP 1	Highest with lowest categories	7	2,154	6,439	OR	0.81(0.61, 1.09)	0.1585	43.13%	0.42	0.81(0.61, 1.09)	0.2816	No
Chi F,2013	IGFBP 2	Highest with lowest categories	3	1,348	2,962	OR	0.76(0.41, 1.43)	0.4016	68.77%	0.02	0.77(0.41, 1.43)	NA	No
Chi F,2013	IGFBP 3	Highest with lowest categories	16	3,755	11,509	OR	0.88 (0.70, 1.10)	0.268	45.74%	0.31	0.88(0.71, 1.10)	0.5968	No
Xu J,2016	HbA1c	Highest vs lowest categories (%)	8	2,137	45,569	RR	1.25(0.93, 1.67)	0.1414	53.83%	0.30	1.25(0.99, 1.67)	NA	No
Xu J,2016	C-peptide	Highest vs lowest categories(ng/ml)	11	3,211	13,888	RR	1.35(0.97, 1.89)	0.0788	70.63%	0.73	1.35(0.97, 1.89)	0.776	No
Micronutrients													
Ma YL,2011	25-hydroxyvitamin D	Highest with lowest categories	10	3,142	7,840	RR	0.67(0.54, 0.83)	0.0002	20.49%	0.79	0.670 (0.541, 0.830)	NA	Suggestive
Ben S,2018	Vitamin B2	Highest with lowest categories	2	1,593	32,962	RR	0.74(0.57, 0.95)	0.02	9.32%	/	0.74(0.58, 0.95)	NA	Weak
Larsson SC, 2010	Vitamin B6	Highest vs lowest categories (pmol/)	4	883	2,207	RR	0.53(0.38, 0.71)	0.0012	0.89%	0.97	0.52(0.38, 0.72)	NA	Weak
Shiao SPK,2018	Vitamin B12	Mean (pmol/L)	8	3,296	8,290	SMD	-0.07(-0.14, -0.004)	0.0384	54.91%	0.03	-0.07(-0.19, 0.05)	0.47	Weak
Zhang D, 2015	Folate	CRC vs healthy controls	12	1,159	2,982	SMD	-1.29(-2.29, -0.30)	0.0105	99.57%	0.0442	-1.29(-3.09, 0.51)	NA	Weak
Dong YH,2017	Vitamin E	Mean (μmol/L)	9	310	5,927	SMD	-0.79(-1.63, 0.05)	0.065	96.61%	0.01	-0.79(-1.63, 0.05)	0.3192	No
Lee JE,2011	1,25-dihydroxyvitamin D	Highest with lowest categories	4	625	1,801	OR	1.01(0.66, 1.59)	0.9302	42.59%	0.64	1.020 (0.656, 1.585)	NA	No
Vinceti M,2018	Selenium	Highest vs. lowest category	8	2,627	712,746	OR	0.86(0.62, 1.18)	0.3509	42.92%	0.7895	0.859(0.624, 1.182)	NA	No

Gumulec J,2014	Serum Zinc	Largest variation among serum levels	5	313	529	SMD	0.05(-3.47, 3.56)	0.9788	99.40%	0.7342	0.05(-3.47, 3.56)	0.00	No
Gumulec J,2014	Tissue Zinc	Largest variation among tissue levels	10	234	398	SMD	-0.76(-3.08, 1.55)	0.5187	98.75%	0.00	-0.76(-3.08, 1.55)	0.1503	No
Other Biomarkers													
Zhang BL,2015	Blood group A	A vs non-A	8	6,931	3,214,941	OR	1.01(0.90, 1.14)	0.8533	75.87%	0.12	1.01(0.90, 1.14)	0.09	No
Zhang BL,2015	Blood group AB	AB vs non-AB	8	6,931	3,191,289	OR	0.94(0.73, 1.21)	0.6416	61.18%	0.44	0.94(0.73, 1.21)	NA	No
Zhang BL,2015	Blood group B	B vs non-B	8	6,931	3,193,532	OR	1.00(0.91, 1.10)	0.9963	18.12%	0.41	1.00(0.91, 1.10)	NA	No
Zhang BL,2015	Blood group O	O vs non-O	8	6,931	3,219,151	OR	0.91(0.84, 1.00)	0.0445	54.58%	0.23	0.91(0.84, 1.00)	NA	Weak
Naing C,2017	Telomere Length	Shortest Q4 vs longest Q2	8	951	2,569	OR	1.02(0.75, 1.40)	0.8842	42.82%	0.34	1.02(0.75, 1.40)	NA	No
Jiang R,2016	Enterolactone	Per doubling (nmol/l)	3	762	2,408	RR	1.14(0.89, 1.47)	0.2924	66.71%	0.06	1.14(0.89, 1.47)	NA	No
Protein & amino acids													
Lu S,2017	Total Adiponectin	Highest vs lowest categories	8	3,420	8,937	RR	0.78(0.65, 0.95)	0.0143	39.81%	0.38	0.79(0.65, 0.95)	0.578	Weak
Yang G,2016	Resistin	Mean (ng/mL)	11	965	2,290	SMD	0.65(0.19, 1.11)	0.0059	94.79%	0.94	0.65(0.19, 1.11)	NA	Weak
Shiao SPK,2018	Homocysteine	Mean (mmol/L)	8	4,047	9,604	SMD	0.13(0.04, 0.21)	0.003	68.35%	0.69	0.13(-0.03, 0.28)	NA	Weak
Yu DD,2018	Angiogenin	Mean (ng/ml)	2	188	240	SMD	1.53(0.52, 2.54)	0.003	87.41%	/	1.53(0.52, 2.54)	NA	Weak
Xing XJ,2014	MMP7	Mean (% total fatty acids)	10	625	1,020	SMD	2.31(0.91, 3.71)	0.0013	98.80%	0.00	2.31(-0.24, 4.86)	0.4128	Weak
Li XX,2014	TLR-4 protein	CRC vs healthy controls	3	168	283	OR	4.75(1.16, 19.45)	0.0304	77.55%	0.01	4.75(1.16, 19.46)	0.0181	Weak
Sun SJ,2016	HER-2 expression	CRC vs healthy controls	13	932	1,453	OR	11.82(5.36, 26.08)	9.33E-10	63.02%	0.00	11.82(5.36, 26.08)	0.103	Weak
Feng Z,2015	Ferritin	Mean (ng/ml)	7	277	927	SMD	-1.57(-3.06, -0.08)	0.0388	98.50%	0.00	-1.57(-3.06, -0.08)	NA	Weak
Ouyang Z,2017	CD26	Tumour cell vs normal cell	9	952	1,809	SMD	-0.33(-4.35, 3.70)	0.8737	99.84%	0.45	-0.33(-7.62, 6.97)	0.0098	No
Gialamas SP,2013	Leptin	Mean	23	3,508	7,478	SMD	0.20(-0.32, 0.72)	0.4551	99.03%	0.58	0.20(-0.75, 1.14)	0.000000	No

CRC: colorectal cancer, CI: confidence interval, HKSJ: Hartung-Knapp-Sidik-Jonkman, [1]PEgger: The P value for small study effect test, [2]Psig: The P value for excess significance test, RR: risk ratio, SMD: standard mean difference, OR: odds ratio, r: standardized correlation coefficient, LC n-3 PUFA: long chain n-3 polyunsaturated fatty acid, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, DPA: Docosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, HPV: Human papillomavirus, H.pylori: Helicobacter pylori, CRP: C-reactive protein, IL-6: Interleukin 6, HOMA-IR: homeostatic model assessment-insulin resistance, IGF 1/2: Insulin-like growth factor 1/2, IGFBP 1/2/3: Insulin-like growth factor-binding protein 1/2/3, HbA1c: glycated hemoglobin, MMP7: matrix metalloproteinase-7, CD26: dipeptidyl peptidase IV.

Supplementary Table 3 Characteristics and main findings of 42 non-overlapped Mendelian randomisation analyses

First author, Year (Citation)	Biomarker (Unit)	Power to detect given effect estimates	Exposure			Outcome			Study design	Main method	Main estimate	P value	Sensitivity analyses	Consistent evidence of a causal effect	Evidence
			Sample size	Population	Variance (R^2) explained by GI (%)	Sample size	Metric	Population							
Micronutrients															
Cornish AJ, 2019	Blood selenium	1.000|OR≤0.75 or OR≥1.33	2,603 participants	Queensland	2	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.85 (0.75, 0.96)	0.008**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Likely non-causal
Cornish AJ, 2019	Blood zinc	1.000|OR≤0.75 or OR≥1.33	2,603 participants	Queensland	4.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.94 (0.86, 1.03)	0.179**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Circulating 25-hydroxyvitamin D	1.000|OR≤0.75 or OR≥1.33	79,366 participants	European	2.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.99 (0.90, 1.09)	0.895**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Circulating carotenoids	1.000|OR≤0.75 or OR≥1.33	1,190 participants	Italian	2.8	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	1.04 (0.94, 1.15)	0.451**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Iron status	0.981|OR≤0.75 or OR≥1.33	48,972 participants	European	1.2	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.17 (1.00, 1.36)	0.049**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Serum calcium	1.000|OR≤0.75 or OR≥1.33	39,400 participants	European	2.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.93 (0.83, 1.05)	0.264**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Serum vitamin A (retinol)	0.879|OR≤0.75 or OR≥1.33	5,006 participants	Finland, US	0.7	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.07 (0.78, 1.47)	0.663**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Serum vitamin B12	1.000|OR≤0.75 or OR≥1.33	45,576 & 37,341 participants	Iceland, Denmark	4.7	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.21 (1.04, 1.42)	0.016**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Likely non-causal
Cornish AJ, 2019	Serum vitamin B6	0.994|OR≤0.75 or OR≥1.33	2,930 participants		1.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	1.04 (0.90, 1.20)	0.592**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Serum vitamin E	0.857|OR≤0.75 or OR≥1.33	5,006 participants	European	0.7	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.94 (0.76, 1.17)	0.600**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Fatty acid/Lipid metabolism biomarkers															

May-Wilson S, 2017	Plasma Arachidic acid (20:0) (GRS)	Limited power (not specified)	38,000 participants	European	/	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.92(0.61, 1.39)	0.700	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
May-Wilson S, 2017	Plasma Palmitic acid (16:0) (GRS)	Limited power (not specified)	38,000 participants	European	0.21-0.98	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.97(0.78, 1.21)	0.820	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
May-Wilson S, 2017	Plasma Stearic acid (18:0) (GRS)	Limited power (not specified)	38,000 participants	European	0.01-1.39 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	1.16(1.01, 1.35)	0.040	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
Liyanage UE, 2019	Plasma DHA 22:6n-3	/	8,866 participants	European	0.65	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Wald-type ratio estimator (combining estimate with those from May-Wilson et al 2017)	1.07(0.84, 1.36)	0.583*	IVW estimate without combining with data from other study (May-Wilson et al 2017)	No	Unknown
Liyanage UE, 2019	Plasma EPA 20:5n-3	/	8,866 participants	European	2.05	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW (combining estimate with those from May-Wilson et al 2017)	1.06(0.91, 1.22)	0.455*	IVW estimate without combining with data from other study (May-Wilson et al 2017)	No	Unknown

Liyanage UE, 2019	Plasma DPA 20:5n-3	/	8,866 participants	European	11.12	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW (combining estimate with those from May-Wilson et al 2017)	1.10(1.01, 1.19)	0.034*	IVW estimate without combining with data from other study (May-Wilson et al 2017)	No	Unknown
Liyanage UE, 2019	Plasma AA 20:4n-6	/	8,631 participants	White adults	33.07	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW (combining estimate with those from May-Wilson et al 2017)	1.05(1.03, 1.07)	2.00E-05*	IVW estimate without combining with data from other study (May-Wilson et al 2017)	No	Evidence of causality
May-Wilson S, 2017	Plasma DGLA (20:3n-6) (GRS)	Limited power (not specified)	38,000 participants	European	2-11.1 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.91(0.83, 1.00)	0.060	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
Liyanage UE, 2019	Plasma LA 18:2n-6	/	8,631 participants	White adults	8.3	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW (combining estimate with those from May-Wilson et al 2017)	0.95(0.93, 0.97)	9.60E-05*	IVW estimate without combining with other study	No	Evidence of causality
May-Wilson S, 2017	Plasma Oleic acid (18:1n-9) (GRS)	Limited power (not specified)	38,000 participants	European	0.32-2.14 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.77(0.65, 0.92)	0.004	Where more than one instrument variant was available: heterogeneity assessment, random-effects IVW MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	Yes	Evidence of causality
May-Wilson S, 2017	Plasma Palmitoleic acid (16:1n-7) (GRS)	Limited power (not specified)	38,000 participants	European	0.01-1.57 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid	0.36(0.15, 0.84)	0.018	Where more than one instrument variant was available: heterogeneity assessment, random-	No	Unknown

										generated for each CRC cohort was combined under fixed-effects models			effects IVW MR; assessing impact of pleiotropy by using IVW and MR-Egger methods		
Liyanage UE, 2019	Plasma ALA 18:3n-3	/	8,866 participants	European	1.03	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Wald-type ratio estimator (combining estimate with those from May-Wilson et al 2017)	0.89(0.78, 1.02)	0.098*	IVW estimate without combining with other study	No	Unknown
Cornish AJ, 2019	HDL	1.000|OR≤0.75 or OR≥1.33	188,577 participants	European	6.1	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.03 (0.92, 1.14)	0.620**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	LDL	1.000|OR≤0.75 or OR≥1.33	188,577 participants	European	7.9	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.14 (1.04, 1.25)	0.006**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Likely non-causal
Cornish AJ, 2019	Mono-unsaturated fatty acids	0.493|OR≤0.75 or OR≥1.33	24,925 participants	European	0.3	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	1.07 (0.78, 1.46)	0.672**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Omega-6 polyunsaturated fatty acids	1.000|OR≤0.75 or OR≥1.33	24,925 participants	European	2.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.15 (0.98, 1.36)	0.095**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Likely non-causal
Cornish AJ, 2019	Total cholesterol	1.000|OR≤0.75 or OR≥1.33	24,925 participants	European	9.5	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.09 (1.01, 1.18)	0.025**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Likely non-causal
Cornish AJ, 2019	Total triglycerides	1.000|OR≤0.75 or OR≥1.33	188,577 participants	European	6.1	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.93 (0.84, 1.04)	0.192**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Inflammatory Markers															
Wang X, 2018	C-reactive protein (19 SNPs)	0.825|OR≥1.12	66,185 & 40,473 participants	European	5	30,480 cases and 22,844 controls	OR per SD	European	Two-sample	IVW	1.04(0.97, 1.12)	0.256	Subgroup analyses stratified by cancer sites and stages, sex, BMI, smoking, NSAID use, aspirin use, history of endoscopy, family history of CRC; Egger regression	No	Unknown
Cornish AJ, 2019	Plasma IL-6 receptor subunit alpha	1.000|OR≤0.75 or OR≥1.33	3,301 participants	European	60.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.98 (0.96, 1.00)	0.035**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Insulin related markers															

Cornish AJ, 2019	Fasting glucose	1.000|OR≤0.75 or OR≥1.33	96,496 participants	European	3.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.04 (0.92, 1.18)	0.519**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Fasting proinsulin	1.000|OR≤0.75 or OR≥1.33	46,186 participants	European	6.1	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.97 (0.90, 1.03)	0.310**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	HbA1C levels	0.999|OR≤0.75 or OR≥1.33	46,368 participants	European	1.8	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.02 (0.85, 1.22)	0.866**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Plasma IGF–I	0.995|OR≤0.75 or OR≥1.33	3301 participants	European	1.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.88 (0.76, 1.01)	0.064**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Other Biomarkers															
Haycock PC, 2017	Telomere length	1	9,190 participants	European	/	14,537 cases and 16,922 controls	OR per SD	European	Two-sample	Maximum likelihood	1.09(0.91, 1.31)	0.340	Heterogeneity analysis, weighted median, MR-Egger	No	Likely non-causal
Protein& amino acid															
Au Yeung SL, 2019	GDF-15	0.8|OR≥1.11 (R2=0.15) or OR≥1.10 (R2=0.21)	5,440 participants	European	15 or 21	4,562 cases and 382,756 controls	OR per SD	European	Two-sample	IVW (Fixed effect)	0.91(0.80, 1.04)	/	Multiplicative random effect IVW; Lead SNP analysis; MR-Egger intercept test; Mendelian randomisation restricted to instruments from the same gene region (PGPEP1 or GDF15)	No	Unknown
Nimptsch K, 2017	Adiponectin (Incorporating the ADIPOQ allele score and plasma adiponectin concentrations)	0.8|OR≤0.76	2,880 participants	European and US	/	1,253 cases and 1,627 controls	OR per score unit	European and US	One-sample	Conditional logistic regression	0.73(0.40, 1.34)	/	Restriction to Caucasians; Effect estimate in different study (HPFS and NHS)	No	Likely non-causal
Cornish AJ, 2019	Blood carnitine	1.000|OR≤0.75 or OR≥1.33	7,824 participants	European	13.9	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.99 (0.92, 1.06)	0.682**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Blood methionine	0.676|OR≤0.75 or OR≥1.33	7,824 participants	European	0.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.92 (0.70, 1.19)	0.505**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Circulating adiponectin	1.000|OR≤0.75 or OR≥1.33	39,883 participants	European	1.8	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.93 (0.81, 1.07)	0.309**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown

Cornish AJ, 2019	Circulating fetuin-A	1.000|OR≤0.75 or OR≥1.33	9,055 & 2,119 participants	European, African American	14.3	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.98 (0.94, 1.02)	0.370**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019	Serum immunoglobulin E	0.997|OR≤0.75 or OR≥1.33	6,819 participants	European	1.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.92 (0.82, 1.03)	0.159**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown

*: statistically significant threshold set up at P≤0.0001; **: statistically significant threshold set up at P≤0.0013, GI: genetic instrument, SNP: Single Nucleotide Polymorphism, OR: odds ratio, HR: hazard ratio, SD: standard deviation, GRS: genetic risk score, BMI: body mass index, IVW: inverse variance weighted, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, DPA: Docosapentaenoic acid, AA: arachidonic acid, DGLA: dihomo-γ-linolenic acid, LA: linoleic acid, ALA: α-Linolenic acid, HDL: high-density lipoprotein cholesterol, LD: linkage disequilibrium, LDL: low-density lipoprotein cholesterol, IL-6: interleukin 6, HbA1C: glycated hemoglobin, IGF-1: insulin-like growth factor 1, GDF-15: Growth differentiation factor 15.

Supplementary Table 4 General characteristics of 145 meta-analyses of observational studies											
First author/Year (citation)	Population	Location	Biomarker	No of cases	No of participants	Unit of comparison	No of studies	Study design	Metric	Model	Effect size (95%CI)
Fatty acid/Lipid metabolism biomarkers											
Yang B,2014[1]	CRC & controls	America Europe Asia	Adipose DHA 22:6 (n-3)	93	204	Mean (% total fatty acids)	2	CC	SMD	Random	0.19(-0.09, 0.47)
Yang B,2014[1]	CRC & controls	America Europe Asia	Adipose DPA 22:5 (n-3)	93	204	Mean (% total fatty acids)	2	CC	SMD	Random	-0.02(-0.35, 0.30)
Yang B,2014[1]	CRC & controls	America Europe Asia	Adipose EPA 20:5 (n-3)	93	204	Mean (% total fatty acids)	2	CC	SMD	Random	-0.07(-0.35, 0.20)
Yang B,2014[1]	General/CRC & controls	America Europe Asia	Biospecimen DHA 22:6 (n-3)	1,315	84,114	Highest vs lowest categories	6	CC/CS	RR	Random	0.68(0.54, 0.84)
Yang B,2014[1]	CRC & controls	America Europe Asia	Biospecimen DHA 22:6 (n-3)	623	1,938	Mean (% total fatty acids)	7	CC	SMD	Random	-0.23(-0.34, -0.11)
Yang B,2014[1]	General/CRC & controls	America Europe Asia	Biospecimen DHA 22:6 (n-3)	675	58,713	Highest vs lowest categories	3	CS	RR	Random	0.76(0.56, 1.01)
Yang B,2014[1]	General/CRC & controls	America Europe Asia	Biospecimen DPA 22:5 (n-3)	446	15,593	Highest vs lowest categories	3	CC/CS	OR	Random	0.80(0.42, 1.52)
Yang B,2014[1]	CRC & controls	America Europe Asia	Biospecimen DPA 22:5 (n-3)	587	1,404	Mean (% total fatty acids)	6	CC	SMD	Random	-0.08(-0.22, 0.06)
Yang B,2014[1]	General/CRC & controls	America Europe Asia	Biospecimen EPA 20:5 (n-3)	1,367	84,223	Highest vs lowest categories	6	CC/CS	RR	Random	0.78(0.64, 0.96)
Yang B,2014[1]	CRC & controls	America Europe Asia	Biospecimen EPA 20:5 (n-3)	623	1,938	Mean (% total fatty acids)	7	CC	SMD	Random	-0.27(-0.41, -0.13)
Yang B,2014[1]	General/CRC & controls	America Europe Asia	Biospecimen EPA 20:5 (n-3)	675	58,713	Highest vs lowest categories	3	CS	RR	Random	0.77(0.58, 1.00)
Yang B,2014[1]	General/CRC & controls	America Europe Asia	Biospecimens LC n-3 PUFA	1,502	60,360	Highest vs lowest categories	7	CC/CS	RR	Random	0.74(0.63, 0.87)
Yang B,2014[1]	CRC & controls	America Europe Asia	Biospecimens LC n-3 PUFA	329	786	Mean (% total fatty acids)	4	CC	SMD	Random	0.22(0.07, 0.37)
Yang B,2014[1]	General/CRC & controls	America Europe Asia	Biospecimens LC n-3 PUFA	675	58,713	Highest vs lowest categories	3	CS	RR	Random	0.76(0.59, 0.97)
Yang B,2014[1]	CRC & controls	America Europe Asia	Blood DHA 22:6 (n-3)	646	1,425	Mean (% total fatty acids)	5	CC	SMD	Random	-0.24(-0.40, -0.10)
Yang B,2014[1]	CRC & controls	America Europe Asia	Blood DPA 22:5 (n-3)	646	1,425	Mean (% total fatty acids)	4	CC	SMD	Random	0.04(- 0.11,0.20)
Yang B,2014[1]	CRC & controls	America Europe Asia	Blood EPA 20:5 (n-3)	283	564	Mean (% total fatty acids)	5	CC	SMD	Random	-0.30(-0.44, -0.15)

Esposito K,2013[2]	General/CRC & controls	America Europe Asia	HDL-cholesterol	1,335	/	Highest vs lowest categories (mg/dl)	9	CC/CS	RR	Random	0.89(0.78, 1.02)
Yao X,2015[3]	General/CRC & controls	North America, Europe, and Asia	HDL-cholesterol	2,542	136,698	Highest vs lowest categories	6	PS	RR	Random	0.84(0.69, 1.02)
Yao X,2015[3]	General/CRC & controls	North America, Europe, and Asia	LDL-cholesterol	1,626	9,175	Highest vs lowest categories	3	PS	RR	Random	1.04(0.60, 1.81)
Yao X,2015[3]	General/CRC & controls	North America, Europe, and Asia	Total cholesterol	10,892	7,725,310	Highest vs lowest categories	10	PS	RR	Random	1.11(1.01, 1.21)
Yao X,2015[3]	General/CRC & controls	North America, Europe, and Asia	Total cholesterol	/	/	100 mg/dL increment	5	PS	RR	Random	1.01(0.97, 1.05)
Esposito K,2013[2]	General/CRC & controls	America Europe Asia	Triglycerides	8,164	/	Highest vs lowest categories (mg/dl)	13	CC/CS	RR	Random	1.06(0.95, 1.17)
Yao X,2015[3]	General/CRC & controls	North America, Europe, and Asia	Triglycerides	8,127	2,252,217	High versus low	9	PS	RR	Random	1.18(1.04, 1.34)
Yao X,2015[3]	General/CRC & controls	North America, Europe, and Asia	Triglycerides	/	/	50 mg/dL increment	3	PS	RR	Fixed	1.01(1.00, 1.03)
Infectious agents											
Repass J,2018[4]	CRC patients (CRC sample with normal tissue)	North America	F. nucleatum	139	139	CRC tissue to adjacent normal tissue	2	CC	r	Random	0.38(0.17, 0.56)
Liu C,2016[20]	H.pylori-infected patients and controls	America Europe Asia	H. pylori infection	5,380	17,189	CRC vs non-CRC	19	NCC/CC/CSS	OR	Random	1.57(1.29, 1.83)
Wang F,2014[6]	CRC & Controls	America Europe Asia	H. pylori infection	3,450	10,808	Infected vs non-infected	17	CC	OR	Fixed	1.28(1.16, 1.41)
Wang F,2014[6]	CRC & Controls	America Europe Asia	H. pylori infection_CagA	/	/	CRC vs non-CRC	6	CC	OR	Fixed	1.22(1.08, 1.37)
Wang X,2017[7]	H.pylori infected and controls	/	H. pylori infection	3,300	16,857	CRC vs non-CRC	10	CC/CSS	OR	Random	1.29(1.06, 1.51)
Zhao Y,2016[8]	CRC & Controls	America Europe Asia Australia	H. pylori infection	1,457	3,762	CRC vs non-CRC	14	CC	OR	Random	1.33(1.01, 1.77)
Wu Q,2013[9]	CRC & Controls	America Europe Asia	H. pylori infection	3,488	7,836	CRC vs non-CRC	20	CC/NCC/CSS	OR	Random	1.39(1.18, 1.64)
Rokkas T,2013[10]	CRC & Controls	America Europe Asia	H. pylori infection	/	/	Infected vs non-infected	17	CC/CSS	OR	Random	1.30(1.07, 1.59)
Guo Y,2014[11]	CRC & Controls	Asia	H. pylori infection	/	/	Infected vs non-infected		CC	OR	Random	1.08(0.89, 1.68)

Zhao YS, 2008[12]	CRC & Controls	America Europe Asia	H. pylori infection	1,709	3,581	CRC vs controls	14	CC/NCC	OR	Random	1.49(1.17, 1.91)
Baandrup L,2017[13]	CRC/CRA tissue and tumour adjacent tissue or cancer free control tissue	America Europe Asia	HPV	699	1,156	Tumour tissue vs normal tissue	8	CC	OR	Random	2.10(1.30, 3.20)
Baandrup L,2017[13]	CRC/CRA tissue and tumour adjacent tissue or cancer free control tissue	America Europe Asia	HPV	419	575	Infected vs non-infected	8	CC	OR	Random	6.00(2.00, 17.90)
Damin DC,2013[14]	CRC & controls	America Europe Asia	HPV	289	393	Infected vs non-infected	5	CC	OR	Random	10.04(3.67, 27.46)
Damin DC,2013[14]	CRC & Controls	America Europe Asia	HPV	/	/	Tumour tissue vs normal tissue	6	CC	OR	Random	4.05(1.79, 9.14)
Pelizzer T,2016[15]	HPV & Controls	America Europe Asia	HPV	126	612	CRC vs non-CRC	4	CC/CSS	OR	Random	4.66(2.50, 8.69)
Zhang XH,2018[16]	CRC & Controls	China	HPV	766	1,236	Tumour tissue vs normal tissue	10	CC	OR	Random	10.78(4.22, 27.53)
Peder LD,2018[17]	CRC & Controls	Brazil	HPV	216	/	Infected vs control	2	CC	RR	Random	2.03(1.77, 2.33)
Ibragimova MK,2018[18]	CRC & Controls	America Europe Asia	HPV	2,049	2,879	Tumour tissue vs Cancer-free tissue	19	CC	RR	Random	2.97(1.42, 6.22)
Bai B,2016[19]	CRC patients	America Europe Asia	Human cytomegalovirus infection	480	960	Tumour tissue vs normal tissue	4	CC	OR	Fixed	6.59(4.48, 9.69)
Liu H,2016[5]	CRC & Controls	Europe Asia	Bacteroides-Prevotella group	97	255	Healthy controls (logarithmic number of bacteria per gram stool)	3	CC	SMD	Random	-0.71(-2.56, 1.14)
Liu H,2016[5]	CRC & Controls	Europe Asia	Bifidobacterium	127	315	Healthy controls (logarithmic number of bacteria per gram stool)	4	CC	SMD	Random	-3.3(-6.57, -0.03)
Liu H,2016[5]	CRC & Controls	Europe Asia	Enterobacteriaceae	37	76	Healthy controls (logarithmic number of bacteria per gram stool)	2	CC	SMD	Random	2.69(0.66, 4.72)

Liu H,2016[5]	CRC & Controls	Europe Asia	Escherichia coli	90	239	Healthy controls (logarithmic number of bacteria per gram stool)	2	CC	SMD	Random	1.4(-1.38, 4.18)
Liu H,2016[5]	CRC & Controls	Europe Asia	Faecalibacterium prausnitzii	86	233	Healthy controls (logarithmic number of bacteria per gram stool)	3	CC	SMD	Random	-0.33(-0.6, 0.05)
Liu H,2016[5]	CRC & Controls	Europe Asia	Lactobacillus	127	315	Healthy controls (logarithmic number of bacteria per gram stool)	4	CC	SMD	Random	-2.72(-5.94, 0.50)
Liu H,2016[5]	CRC & Controls	Europe Asia	Total bacteria	86	233	Healthy controls (logarithmic number of bacteria per gram stool)	3	CC	SMD	Random	0.23(-0.54, 1.00)
Boleij A,2011[21]	S. bovis–infected patients	/	Streptococcus bovis	189	340	CRC vs non-CRC	6	case-series	OR	Fixed	7.26(3.94, 13.36)
Krishnan S,2014[22]	CRC & controls	/	Streptococcus bovis in faeces	148	414	/	3	CC	OR	Random	2.46(0.72, 8.46)
Inflammatory Markers											
Guo YZ,2013[23]	General	America Europe	CRP	1,140	135,794	Per natural log unit change	7	CS	HR	Random	1.10(0.97, 1.23)
Zhou B,2014[24]	General/CRC & controls	America Europe Asia	CRP	4,779	152,942	1-unit change in ln(mg/l)	17	CS/NCC	RR	Random	1.12(1.05, 1.21)
Tsilidis KK, 2008[25]	General/CRC & controls	America Europe Asia	CRP	1,159	39,145	1-unit increase in ln-transformed (mg/L)	8	NCC/CS	OR	Random	1.12(1.01, 1.25)
Zhou B,2014[24]	General/CRC & controls	America Europe Asia	IL-6	1,125	9,909	1-unit change in ln (pg/ml)	6	CS/NCC	RR	Random	1.10(0.88, 1.36)
Kakourou A,2015[26]	General/CRC & controls	America Europe	IL-6	1,308	9,728	Per 1 U change in ln pg/mL	7	CC/CS/NCC	RR	Random	1.10(0.94, 1.28)
Insulin related biomarkers											
Xu J,2016[27]	CRC & Controls	America Europe Asia	C peptide	3,191	1,375,980	Highest vs lowest categories(ng/ml)	9	CC/NCC	RR	Random	1.27(1.08, 1.49)

Pisani, 2008[28]	General/CRC & controls	/	C peptide	1,309	5,542	Highest vs lowest categories	12	CC/NCC/CS	RR	Fixed	1.35(1.13, 1.61)
Chen L,2013[29]	CRC & Controls	America Europe Asia	C peptide	3,109	7,394	Highest vs lowest categories	9	NCC	OR	Random	1.39(1.04, 1.87)
Xu J,2016[27]	General/CRC & controls	America Europe Asia	HbA1c	2,137	820,317	Highest vs lowest categories (%)	8	CC/NCC/CS	RR	Fixed	1.22(1.02, 1.47)
Xu J,2016[27]	General/CRC & controls	America Europe Asia	HOMA-IR	2,956	347,326	Highest vs lowest categories (fasting glucose (mmol/L) × fasting insulin (mIU/L) / 22.5)	8	CC/NCC/CS	OR	Fixed	1.47(1.24, 1.74)
Xu J,2016[27]	General/CRC & controls	America Europe Asia	Fasting insulin	3,239	354,870	Highest vs lowest categories (mIU/L)	10	CC/NCC/CS	OR	Fixed	1.42(1.19, 1.69)
Xu J,2016[27]	General/CRC & controls	America Europe Asia	Fasting glucose	17,764	3,805,861	Highest vs lowest categories (mmol/L)	18	CC/NCC/CS	OR	Random	1.12(1.06, 1.18)
Shi J,2015[30]	General/CRC & controls	/	Fasting glucose	62,814	2,969,306	Per 20 mg/dL increase	6	CC/CS/NCC	RR	Fixed	1.02(1.01, 1.02)
Shi J,2015[30]	General/CRC & controls	/	Fasting glucose	62,814	2,969,306	Highest vs lowest categories (FPG category ≥ 3)	6	CC/CS/NCC	RR	Fixed	1.15(1.02, 1.31)
Shi J,2015[30]	General/CRC & controls	/	Fasting glucose	/	/	Highest vs lowest categories (FPG category ≥=2)	5	CC/CS/NCC	RR	Random	1.57(1.31, 1.89)
Crawley DJ,2014[31]	/	America Europe Asia	Fasting glucose	908	/	'high' and 'normal' <6.1 mmol/L cut off	5	CC/CS	RR	Random	1.35(1.21, 1.51)
Pisani, 2008[28]	General/CRC & controls	/	Fasting glucose	1,741	1,381,741	Highest vs lowest categories	11	CC/NCC/CS	RR	Fixed	1.18(1.07, 1.31)
Chi F,2013[32]	CRC & Controls	Caucasians, Asian, mixed population	IGF 1	3,807	11,613	Highest vs lowest categories	16	CC/NCC	OR	Fixed	1.25(1.08, 1.45)
Rinaldi S,2010[33]	CRC & Controls	Europe	IGF I	1,741	5,586	1 standard deviation change of average IGF-I distribution	10	CC/CS	RR	Random	1.10(1.01, 1.19)
Morris J, 2006[34]	CRC & Controls	America, Europe, Asia	IGF 1	1,106	3,501	Highest vs lowest categories	7	NCC	OR	Random	1.37(1.05, 1.78)
Chi F,2013[32]	CRC & Controls	Caucasians, Asian, mixed population	IGF 2	783	4,007	Highest vs lowest categories	6	CC/NCC	OR	Fixed	1.52(1.16, 2.01)

Morris J, 2006[34]	CRC & Controls	America, Europe, Asia	IGF 2	384	1,685	Highest vs lowest categories	3	NCC	OR	Random	1.95(1.26, 3.00)
Chi F,2013[32]	CRC & Controls	Caucasians, Asian, mixed population	IGFBP 1	2,154	6,439	Highest vs lowest categories	7	CC/NCC	OR	Fixed	0.85(0.70, 1.03)
Chi F,2013[32]	CRC & Controls	Caucasians, Asian, mixed population	IGFBP 2	1,348	2,962	Highest vs lowest categories	3	CC/NCC	OR	Random	0.77(0.41, 1.43)
Chi F,2013[32]	CRC & Controls	Caucasians, Asian, mixed population	IGFBP 3	3,755	11,509	Highest vs lowest categories	15	CC/NCC	OR	Random	0.88(0.71, 1.10)
Morris J, 2006[34]	CRC & Controls	America, Europe, Asia	IGFBP 3	1,106	3,501	Highest vs lowest categories	7	NCC	OR	Random	0.98(0.64, 1.51)
Micronutrients											
Chuang SC,2013[35]	CRC & Controls	America Europe	Folate	3,477	10,516	Dose-response (per 10 nmol/L)	8	CS	RR	Fixed	0.94(0.88, 1.01)
Chuang SC,2013[35]	CRC & Controls	America Europe	Folate	3,477	10,516	Highest vs lowest categories	8	CS	RR	Fixed	0.91(0.77, 1.05)
Shiao SPK,2018[36]	CRC & Controls	Europe, Asia	Folate	1,466	3,393	Mean (nmol/L)	8	CC	SMD	Random	-0.46(-0.92, -0.00)
Shiao SPK,2018[36]	CRC & Controls	Europe, Caucasian, Asia	Folate	3,515	8,764	Mean (nmol/L)	9	CS	SMD	Random	0.01(-0.06, 0.08)
Moazzen S,2017[37]	CRC & Controls	/	Folate	/	/	/	22	CC	RR	Random	0.85(0.85, 1.30)
Zhang D, 2015[38]	CRC & Controls	/	Folate	1,181	3,139	CRC vs healthy controls	11	CC	SMD	Random	-1.10(-1.60, -0.60)
Shiao SPK,2018[36]	CRC & Controls	Europe, Asia	Vitamin B12	360	1,068	Mean (pmol/L)	6	CC	SMD	Random	-0.99(-1.74, 0.25)
Shiao SPK,2018[36]	CRC & Controls	Europe, Caucasian	Vitamin B12	3,299	8,309	Mean (pmol/L)	8	CS	SMD	Random	-0.04(-0.09, 0.00)
Sun NH,2016[39]	CRC & Controls	Europe USA	Vitamin B12	/	/	Per 150 pmol/l increment	3	CC	RR	Random	1.02(0.88, 1.19)
Sun NH,2016[39]	CRC & Controls	Europe USA	Vitamin B12	682	1,732	Highest vs lowest categories	3	CC	RR	Fixed	0.93(0.56, 1.53)
Zhang D, 2015[38]	CRC & Controls	/	Vitamin B12	873	2,198	CRC vs healthy controls	10	CC	OR	Random	-28.52(-50.60, -6.43)
Shiao SPK,2018[36]	CRC & Controls	Globe	Vitamin B2	1,643	4,240	Mean (nmol/L)	3	CS	SMD	Random	0.00(-0.05, 0.07)
Ben S, 2018[40]	General/CRC & controls	Europe	Vitamin B2	1,593	32,962	Highest vs lowest categories	2	NCC	RR	Fixed	0.74(0.59, 0.92)
Shiao SPK,2018[36]	CRC & Controls	Globe	Vitamin B6	2,658	7,361	Mean (nmol/L)	5	CS	SMD	Random	-0.06(-0.11, 0.01)
Larsson SC,2010[41]	General	America Europe	Vitamin B6	883	2,207	Highest vs lowest categories (pmol/)	4	PS	RR	Random	0.52(0.38, 0.71)
Larsson SC,2010[41]	General	America Europe	Vitamin B6	883	2,207	100pmol/mL increment	4	PS	RR	Random	0.51(0.38, 0.69)
Mocellin S,2017[42]	CRC & Controls	Europe USA	Vitamin B6	425	/	Highest vs lowest categories	5	RS	RR	Random	0.56(0.46, 0.67)

Mocellin S,2017[42]	CRC & Controls	Europe USA	Vitamin B6	2,203	/	Per 100 nmol/L decrease	5	RS	RR	Random	0.52(0.43, 0.64)
Vinceti M,2014[43]	General	US Netherlands Finland	selenium	762	383,137	Highest vs lowest categories	5	CS/NCC	OR	Random	0.89(0.65, 1.23)
Vinceti M,2018[44]	General	Europe USA	selenium	2,627	712,746	Highest vs lowest categories	5	CS/NCC	OR	/	0.82(0.72, 0.94)
Chung M,2011[45]	General/CRC & controls	/	25-hydroxyvitamin D	1,127	2,249	Per 10-nmol/L increase	9	NCC	OR	Random	0.94(0.91, 0.97)
Ekmekcioglu C,2017[46]	CRC & Controls	Europe USA	25-hydroxyvitamin D	/	/	20–30 ng/mL 25(OH)D status vs those in the lowest category	24	CC/CS	RR	Fixed	0.83(0.76, 0.90)
Ekmekcioglu C,2017[46]	CRC & Controls	Europe USA	25-hydroxyvitamin D	/	/	Highest vs lowest categories	24	CC/CS	RR	Fixed	0.62(0.56, 0.70)
Gandini S,2011[47]	General/CRC & controls	Europe USA	25-hydroxyvitamin D	2,630	/	10 ng/ml increase	9	CC/NCC	SRR	Random	0.85(0.79, 0.91)
Garland CF,2017[48]	CRC & Controls	/	25-hydroxyvitamin D	6,691	175,127	Highest vs lowest categories	15	NCC	OR	Random	0.67(0.59, 0.76)
Ma Y,2011[49]	CRC & controls	America Europe Asia	25-hydroxyvitamin D	3,142	7,840	Highest vs lowest categories	9	CS/NCC	RR	Random	0.67(0.54, 0.80)
Ma Y,2011[49]	CRC & controls	America Europe Asia	25-hydroxyvitamin D	2,767	6,715	10 ng/mL increment	9	CS/NCC	RR	Random	0.74(0.63, 0.89)
Touvier M,2011[50]	CRC & Controls	/	25-hydroxyvitamin D	2,318	/	Per 100 IU/L increment	6	NCC	RR	Random	0.96(0.94, 0.97)
Lee JE,2011[51]	CRC & Controls	America Europe Asia	25-hydroxyvitamin D	2,622	6,560	Highest vs lowest categories	9	PS	OR	Random	0.66(0.54, 0.81)
Lee JE,2011[51]	CRC & Controls	America Europe	1,25-dihydroxyvitamin D	625	1,801	Highest vs lowest categories	4	PS	OR	Random	1.01(0.59, 1.73)
Yin L, 2009[52]	General/CRC & controls	America Europe Asia	25-hydroxyvitamin D	984	2,944	Per 20 ng ⁄mL increase in serum 25(OH)D	7	NCC/CS	OR	Random	0.57(0.43, 0.76)
Dong Y,2017[53]	General/CRC & controls	Caucasian Asian	Vitamin E	520	6,440	Mean (μmol/L)	10	CC	WMD	Random	-3.00(-4.40, -1.59)
Gumulec J,2014[54]	CRC & Controls	/	Serum Zinc	313	529	Largest variation among serum levels	5	CC	SMD	Random	0.04(-2.57, 2.64)
Gumulec J,2014[54]	CRC & Controls	/	Tissue Zinc	234	398	Largest variation among tissue levels	7	CC	SMD	Random	0.37(-0.97, 1.72)
Other Biomarkers											

Jiang R,2016[55]	CRC & Controls	Canada Europe Asia	Enterolactone	762	2,408	Per doubling (nmol/l)	3	PS	RR	Random	1.04(0.98, 1.10)
Zhang BL,2015[56]	General/CRC & controls	/	Blood group A	6,931	3,214,941	A vs non-A	8	CC/CS	OR	Fixed	1.05(0.98, 1.13)
Zhang BL,2015[56]	General/CRC & controls	/	Blood group AB	6,931	3,191,289	AB vs non-AB	8	CC/CS	OR	Random	1.07(0.88, 1.26)
Zhang BL,2015[56]	General/CRC & controls	/	Blood group B	6,931	3,193,532	B vs non-B	8	CC/CS	OR	Random	1.12(0.94, 1.29)
Zhang BL,2015[56]	General/CRC & controls	/	Blood group O	6,931	3,219,151	O vs non-O	8	CC/CS	OR	Random	0.89(0.81, 0.96)
Zhang X,2017[57]	General	Europe, North America	Telomere Length	319	/	Longest or shortest TL group	2	PS	OR	Random	1.01(0.68, 1.50)
Naing C,2017[58]	General/CRC & controls	America Europe Asia	Telomere Length	951	2,569	Shortest Q4 vs longest Q1	4	NCC	OR	Fixed	1.01(0.77, 1.34)
Naing C,2017[58]	General/CRC & controls	America Europe Asia	Telomere Length	4,000	10,375	Shortest Q4 vs longest Q1	4	CC	OR	Random	1.65(0.96, 2.83)
Protein&amino acids											
Lu S,2017[59]	CRC & Controls	Caucasian	Adiponectin	4,076	9,585	Highest vs lowest categories	8	NCC	RR	Fixed	0.81(0.71, 0.93)
Lu S,2017[59]	CRC & Controls	Caucasian	Adiponectin	4,076	9,585	Per 5 μg/mL increase (dose reponse)	8	NCC	RR	Fixed	0.86(0.77, 0.95)
Lu W,2018[60]	CRC & Controls	/	Adiponectin	7,554	17,352	Mean (μg/mL)	31	CC	WMD	Random	-0.76(-1.20, -0.32)
Xu XT,2011[61]	CRC & Controls	America Europe Asia	Adiponectin	1,343	2,996	Mean (μg/mL)	11	CC/CSS /NCC	WMD	Random	-1.08(-1.84, -0.33)
Joshi RK,2014[62]	CRC & Controls	/	Adiponectin	3,416	8,265	μg/mL	10	CC/CSS /NCC	OR	Random	1.03(0.72, 1.47)
An W,2012[63]	CRC & Controls	America Europe Asia	Adiponectin	488	827	Mean (μg/mL)	10	CC/NC C	WMD	Random	-1.51(-2.42, -0.59)
Joshi RK,2014[62]	CRC & Controls	/	Adiponectin	3,416	11,681	Reference group and compared group (μg/mL)	9	CC/NC C/CSS	OR	Fixed	0.91(0.83, 1.00)
Yu D,2018[64]	CRC & Controls	Japan UK	Angiogenin	188	240	Mean (ng/ml)	2	CC	SMD	Random	1.54(0.50, 2.59)
Yang G,2016[65]	CRC & Controls	/	Resistin	965	3,255	Mean (ng/mL)	11	CC/CS	WMD	Random	1.47(0.78, 2.16)
Joshi RK,2014[62]	CRC & Controls	/	Leptin	/	/	ng/mL	9	CC/CSS /NCC	OR	Random	1.36(0.95, 1.94)
Gialamas SP,2013[66]	CRC & Controls	America Europe Asia	Leptin	3,508	7,478	Mean	23	CC/CS/ CSS/NC C	SMD	Random	0.18(-0.04, 0.40)

Gialamas SP,2013[66]	CRC & Controls	Europe Asia	Leptin	/	/	Highest vs lowest categories	10	CC/CSS /NCC	RR	Random	1.04(0.65, 1.65)
Joshi RK,2014[62]	CRC & Controls	/	Leptin	2,597	6,077	Reference group and compared group (ng/mL)	8	CC/NC C/CSS	OR	Random	1.06(0.87, 1.28)
Feng Z, 2015[67]	CRC & Controls	Europe Asia	Ferritin	277	927	Mean (ng/ml)	6	CC	SMD	Random	-1.57(-2.72, -0.42)
Shiao SPK,2018[36]	CRC & Controls	Europe, Asia	Homocysteine	2,438	5,419	Mean (mmol/L)	10	CC	SMD	Random	0.71(0.41, 1.02)
Shiao SPK,2018[36]	CRC & Controls	Europe, Caucasian	Homocysteine	4,047	9,604	Mean (mmol/L)	8	CS	SMD	Random	0.11(0.02, 0.21)
Zhang DH, 2015[38]	CRC & Controls	/	Homocysteine	3,954	8,992	CRC vs healthy controls	22	CC	OR	Random	2.63 (1.74, 3.51)
Shiao SPK,2018[36]	CRC & Controls	Europe	Methionine	1,980	5,493	Mean (mmol/L)	2	CC	SMD	Random	-0.29(-0.56, 0.02)
Sun SJ,2016[68]	CRC & Controls	Asia Caucasians Africa	HER-2(human epidermal growth factor receptor 2) expression	932	1,453	Categories	13	CC	OR	Random	10.44(5.50, 19.81)
Xing XJ,2014[69]	CRC & Controls	Europe Asia	MMP7	625	1,020	Mean (% total fatty acids)	7	CC	SMD	Random	2.15(1.46, 2.84)
Li XX,2014[70]	CRC & Controls	Asian	TLR-4 protein	168	283	CRC vs healthy controls	3	CC	OR	Random	4.75(1.16, 19.36)
Ouyang Z,2017[71]	CRC & Controls	Asian Caucasian	CD26	952	1,809	Tumour cell vs normal cell	7	CC	SMD	Random	-0.33(-2.97, 2.30)
Ouyang Z,2017[71]	CRC & Controls	Asian	CD26	239	421	Tumour cell vs normal cell	3	CC	SMD	Random	3.94(1.55, 6.33)
Ouyang Z,2017[71]	CRC & Controls	Caucasian	CD26	475	1,150	Tumour cell vs normal cell	4	CC	SMD	Random	-3.77(-7.67, 0.12)

CRC: colorectal cancer, RR: risk ratio, SMD: standard mean difference, OR: odds ratio, r: standardized correlation coefficient, CC: case-control study, CS: cohort study, NCC: nested case-control study, CSS: cross-sectional study, PS: prospective study, LC n-3 PUFA: long chain n-3 polyunsaturated fatty acid, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, DPA: Docosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, HPV: Human papillomavirus, CRP: C-reactive protein, IL-6: Interleukin 6, HOMA-IR: homeostatic model assessment-insulin resistance, IGF 1/2: Insulin-like growth factor 1/2, IGFBP 1/2/3: Insulin-like growth factor-binding protein 1/2/3, HbA1c: glycated hemoglobin, MMP7: matrix metalloproteinase-7, CD26: dipeptidyl peptidase IV.

Supplementary Table 5 Characteristics and main findings of 66 Mendelian randomisation analyses

First author, Year (Citation)	Biomarker (Unit)	Power to detect given effect estimates	Exposure			Outcome			Study design	Main method	Main estimate	P value	Sensitivity analyses	Consistent evidence of a causal effect	Evidence
			Sample size	Population	Variance (R^2) explained by GI (%)	Sample size	Metric	Population							
Micronutrients															
He Y,2018[72]	25-hydroxyvitamin D (log-transformed nmol/L)	0.72|OR=0.83	2,821 participants	European	2.84	10,725 cases, 30,794 controls	OR per SD	European	One-sample	Coefficient ratio method (Weighted GRS adjusted age, sex and BMI)	1.03(0.51,2.07)	0.931	Without adjustment for age, sex and BMI; unweighted GRS	No	Unknown
He Y,2018[72]	25-hydroxyvitamin D (log-transformed nmol/L)	0.93|OR=0.83	77,354 participants	European	2.84	18,967 cases,48,168 controls	OR per SD	European	Two-sample	IVW	0.91(0.69,1.19)	0.475	Weighted median, MR-Egger, robust regression, as well as linear regression, different combinations of SNPs	No	Unknown
Chandler PD, 2018[73]	25-hydroxyvitamin D (GRS)	/	1,782 participants	European women	/	329 cases and 23,294 participants	HR per score unit	European women	One-sample	Age-adjusted Cox-proportional hazard regression by using unweighted GRS (continuous)	1.06(1.00,1.13)	0.070	Categorical assessment of the GRS (0–5 (reference group), 6–7 and 8–10 points), adjustment for BMI, exclusion of one SNP and reporting HR per 20 nmol/L increase in 25(OH)D	No	Unknown
Dimitrakopoulou V, 2017[74]	25-hydroxyvitamin D (weighted multi-polymorphism score)	≥0.8|OR≤0.85 (OR≥1.18) (R^2=0.05) or OR≤0.81 (OR≥1.23) (R^2=0.03)	4501 & 33,996 participants	European	3 to 5	11488 cases and 11679 controls	OR per 25nmol/L increase	European	Two-sample	IVW and likelihood-based method	IVW: 0.92(0.76,1.10) Likelihood: 0.92 (0.76, 1.10)	IVW: 0.36; Likelihood: 0.36	Colorectal cancer in men and women, colon cancer, rectal cancer, proximal colon cancer, distal colon cancer; MR-Egger, weighted median approach, and over-identification tests; Two separate allelic scores: vitamin D synthesis allele score and metabolism allele score	No	Unknown
Dimitrakopoulou V, 2017[74]	25-hydroxyvitamin D (weighted multi-polymorphism score)	≥0.8|OR≤0.85 (OR≥1.18) (R^2=0.05) or OR≤0.81 (OR≥1.23) (R^2=0.03)	4501 & 33,996 participants	European	3 to 5	5100 cases and 4831 controls	OR per 25nmol/L increase	European	Two-sample	IVW and likelihood-based method	IVW: 1.04 (0.78, 1.38); Likelihood: 1.04 (0.78, 1.38)	IVW: 0.81; Likelihood: 0.81	Colorectal cancer in men and women, colon cancer, rectal cancer, proximal colon cancer, distal colon cancer; MR-Egger, weighted median approach, and over-identification tests; Two separate allelic scores: vitamin D synthesis allele score and metabolism allele score	No	Unknown

Theodoratou E, 2012[75]	25-hydroxyvitamin D (GRS)	<0.35	2001 cases and 2237 controls	Scottish	3.6-5.2	2001 cases and 2237 controls	OR per 1ng/ml increase	Scottish	One-sample	Logistic regression	1.16 (0.60,2.23)	/	Unadjusted age and sex; formed three different allele scores	No	Unknown
Ong JS,2018[76]	25-hydroxyvitamin D	/	4501 & 33,996 & 8,711 participants	European	3.5	4,442 cases and 264,638 controls	OR per score unit	European	Two-sample	IVW	0.94(0.79,1.13)	0.520	Meta-analysed UK-Biobank individual cancer estimates with those previously published using data from various studies and consortia	No	Unknown
Cornish AJ, 2019[77]	Blood selenium	1.000|OR≤0.75 or OR≥1.33	2,603 participants	Queensland	2	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.85 (0.75-0.96)	0.008**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	*Likely non-causal*
Cornish AJ, 2019[77]	Blood zinc	1.000|OR≤0.75 or OR≥1.33	2,603 participants	Queensland	4.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.94 (0.86-1.03)	0.179**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Circulating 25-hydroxyvitamin D	1.000|OR≤0.75 or OR≥1.33	79,366 participants	European	2.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.99 (0.90-1.09)	0.895**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Circulating carotenoids	1.000|OR≤0.75 or OR≥1.33	1,190 participants	Italian	2.8	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	1.04 (0.94-1.15)	0.451**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Iron status	0.981|OR≤0.75 or OR≥1.33	48,972 participants	European	1.2	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.17 (1.00-1.36)	0.049**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Serum calcium	1.000|OR≤0.75 or OR≥1.33	39,400 participants	European	2.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.93 (0.83-1.05)	0.264**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Serum vitamin A (retinol)	0.879|OR≤0.75 or OR≥1.33	5,006 participants	Finland, US	0.7	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.07 (0.78-1.47)	0.663**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Serum vitamin B12	1.000|OR≤0.75 or OR≥1.33	45,576 & 37,341 participants	Iceland, Denmark	4.7	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.21 (1.04-1.42)	0.016**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	*Likely non-causal*
Cornish AJ, 2019[77]	Serum vitamin B6	0.994|OR≤0.75 or OR≥1.33	2,930 participants	/	1.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	1.04 (0.90-1.20)	0.592**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown

Cornish AJ, 2019[77]	Serum vitamin E	0.857|OR≤0.75 or OR≥1.33	5,006 participants	European	0.7	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.94 (0.76-1.17)	0.600**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Fatty acid/Lipid metabolism biomarkers															
May-Wilson S, 2017[78]	Plasma Arachidic acid (20:0) (GRS)	Limited power (not specified)	38,000 participants	European	/	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.92(0.61,1.39)	0.700	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
May-Wilson S, 2017[78]	Plasma Palmitic acid (16:0) (GRS)	Limited power (not specified)	38,000 participants	European	0.21-0.98	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.97(0.78,1.21)	0.820	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
May-Wilson S, 2017[78]	Plasma Stearic acid (18:0) (GRS)	Limited power (not specified)	38,000 participants	European	0.01-1.39 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	1.16(1.01,1.35)	0.040	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
May-Wilson S, 2017[78]	Plasma DHA (22:6n-3) (GRS)	Limited power (not specified)	38,000 participants	European	0.7	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	1.32(0.94,1.87)	0.110	Where more than one instrument variant was available: heterogeneity assessment, random-effects IVW MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown

Liyanage UE, 2019[79]	Plasma DHA 22:6n-3	/	8,866 participants	European	0.65	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Wald-type ratio estimator (combining estimate with those from May-Wilson et al 2017)	1.07(0.84,1.36)	0.583*	IVW estimate without combining with data from other study (May-Wilson et al 2017)	No	Unknown
May-Wilson S, 2017[78]	Plasma DPA (22:5n-3) (GRS)	Limited power (not specified)	38,000 participants	European	2.8-8.6 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	1.58(0.99,2.52)	0.060	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
Liyanage UE, 2019[79]	Plasma EPA 20:5n-3	/	8,866 participants	European	2.05	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW (combining estimate with those from May-Wilson et al 2017)	1.06(0.91,1.22)	0.455*	IVW estimate without combining with data from other study (May-Wilson et al 2017)	No	Unknown
May-Wilson S, 2017[78]	Plasma EPA (20:5n-3) (GRS)	<0.1	38,000 participants	European	0.4	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.39(0.13,1.21)	0.100	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
Liyanage UE, 2019[79]	Plasma DPA 20:5n-3	/	8,866 participants	European	11.12	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW (combining estimate with those from May-Wilson et al 2017)	1.10(1.01,1.19)	0.034*	IVW estimate without combining with data from other study (May-Wilson et al 2017)	No	Unknown

May-Wilson S, 2017[78]	Plasma AA (20:4n-6) (GRS)	Limited power (not specified)	38,000 participants	European	0.1-37.6 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	1.05(1.02,1.07)	1.70E-04	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	Yes	Evidence of causality
Liyanage UE, 2019[79]	Plasma AA 20:4n-6	/	8,631 participants	White adults	33.07	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW (combining estimate with those from May-Wilson et al 2017)	1.05(1.03,1.07)	2.00E-05*	IVW estimate without combining with data from other study (May-Wilson et al 2017)	No	Unknown
May-Wilson S, 2017[78]	Plasma DGLA (20:3n-6) (GRS)	Limited power (not specified)	38,000 participants	European	2-11.1 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.91(0.83,1.00)	0.060	Where more than one instrument variant was available: heterogeneity assessment, random-effects inverse-variance weighted MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
May-Wilson S, 2017[78]	Plasma LA (18:2n-6) (GRS)	Limited power (not specified)	38,000 participants	European	0.2-18.1 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.95(0.93,0.98)	3.70E-04	Where more than one instrument variant was available: heterogeneity assessment, random-effects IVW MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	Yes	Evidence of causality
Liyanage UE, 2019[79]	Plasma LA 18:2n-6	/	8,631 participants	White adults	8.3	4,545 cases and 270,342 controls combined 9,254 cases	OR per SD	European	Two-sample	IVW (combining estimate with those from May-Wilson et al 2017)	0.95(0.93,0.97)	9.60E-05*	IVW estimate without combining with other study	No	Unknown

						and 18,386 controls									
May-Wilson S, 2017[78]	Plasma Oleic acid (18:1n-9) (GRS)	Limited power (not specified)	38,000 participants	European	0.32-2.14 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.77(0.65,0.92)	0.004	Where more than one instrument variant was available: heterogeneity assessment, random-effects IVW MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	Yes	Evidence of causality
May-Wilson S, 2017[78]	Plasma Palmitoleic acid (16:1n-7) (GRS)	Limited power (not specified)	38,000 participants	European	0.01-1.57 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Meta-analysis of statistics for each specific fatty acid generated for each CRC cohort was combined under fixed-effects models	0.36(0.15,0.84)	0.018	Where more than one instrument variant was available: heterogeneity assessment, random-effects IVW MR; assessing impact of pleiotropy by using IVW and MR-Egger methods	No	Unknown
Liyanage UE, 2019[79]	Plasma ALA 18:3n-3	/	8,866 participants	European	1.03	4,545 cases and 270,342 controls combined 9,254 cases and 18,386 controls	OR per SD	European	Two-sample	Wald-type ratio estimator (combining estimate with those from May-Wilson et al 2017)	0.89(0.78,1.02)	0.098*	IVW estimate without combining with other study	No	Unknown
Rodriguez-Broadbent H, 2017[80]	Total cholesterol (GRS)	/	188,577 participants	European	8-11 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW	1.46(1.20,1.79)	1.68E-04	Restricted allele score based on SNPs exclusively associated with total cholesterol; LD regression; MR-Egger; omission two strongest SNPs	Yes	Evidence of causality
Rodriguez-Broadbent H, 2017[80]	Triglyceride (GRS)	0.13	188,577 participants	European	8-11 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW	0.98(0.85,1.12)	0.752	Restricted allele score based on SNPs exclusively associated with triglyceride; LD regression; MR-Egger	No	Unknown
Orho-Melander M, 2018[81]	Triglyceride (GRS)	0.8|OR≥1.77	96,598 participants	European	4.9	497 cases, 26,904 participants	OR per SD	Swedish	Two-sample	Logistic regression	1.16(0.78,1.74)	/	Multivariable MR analysis adjusting for the three lipid traits.	No	Unknown
Rodriguez-Broadbent H, 2017[80]	LDL (GRS)	0.68	188,577 participants	European	8-11 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW	1.05(0.92,1.18)	0.485	Restricted allele score based on SNPs exclusively associated with LDL; LD regression; MR-Egger	No	Unknown

Orho-Melander M, 2018[81]	LDL (GRS)	0.8|OR≥1.61	95,454 participants	European	7.1	497 cases, 26,904 participants	OR per SD	Swedish	Two-sample	Logistic regression	1.18(0.85,1.65)	/	Multivariable MR analysis adjusting for the three lipid traits.	No	Unknown
Orho-Melander M, 2018[81]	HDL (GRS)	0.8|OR≥1.68	99,900 participants	European	6	497 cases, 26,904 participants	OR per SD	Swedish	Two-sample	Logistic regression	0.92(0.65,1.33)	/	Multivariable MR analysis adjusting for the three lipid traits.	No	Unknown
Rodriguez-Broadbent H, 2017[80]	HDL (GRS)	0.31	188,577 participants	European	8-11 per SNP	9,254 cases and 18,386 controls	OR per SD	European	Two-sample	IVW	0.94(0.84,1.05)	0.273	Restricted allele score based on SNPs exclusively associated with HDL; LD regression; MR-Egger	No	Unknown
Cornish AJ, 2019[77]	HDL	1.000|OR≤0.75 or OR≥1.33	188,577 participants	European	6.1	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.03 (0.92-1.14)	0.620**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	LDL	1.000|OR≤0.75 or OR≥1.33	188,577 participants	European	7.9	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.14 (1.04-1.25)	0.006**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	*Likely non-causal*
Cornish AJ, 2019[77]	Mono-unsaturated fatty acids	0.493|OR≤0.75 or OR≥1.33	24,925 participants	European	0.3	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	1.07 (0.78-1.46)	0.672**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Omega-6 polyunsaturated fatty acids	1.000|OR≤0.75 or OR≥1.33	24,925 participants	European	2.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.15 (0.98-1.36)	0.095**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Likely non-causal
Cornish AJ, 2019[77]	Total cholesterol	1.000|OR≤0.75 or OR≥1.33	24,925 participants	European	9.5	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.09 (1.01-1.18)	0.025**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	*Likely non-causal*
Cornish AJ, 2019[77]	Total triglycerides	1.000|OR≤0.75 or OR≥1.33	188,577 participants	European	6.1	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.93 (0.84-1.04)	0.192**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Inflammatory Markers															
Nimptsch K, 2015[82]	C-reactive protein (Unweighted GRS)	/	727 participants	European	2 to 3	727 cases and 727 controls	OR per 2-fold higher	European	One-sample	Conditional logistic regression	1.74(1.06,2.85)	/	Investigation for sex-specific associations; adjustments for observationally measured smoking, education, alcohol consumption, dietary intake and physical activity influenced the risk estimates; probit regression models, analysis of individual single-nucleotide polymorphisms; using weighted GRS or Haplotype frequency as instrumental variable	No	Unknown

Wang X, 2018[83]	C-reactive protein (19 SNPs)	0.825|OR≥1.12	66,185 & 40,473 participants	European	5	30,480 cases and 22,844 controls	OR per SD	European	Two-sample	IVW	1.04(0.97,1.12)	0.256	Subgroup analyses stratified by cancer sites and stages, sex, BMI, smoking, NSAID use, aspirin use, history of endoscopy, family history of CRC; Egger regression	No	Unknown
Cornish AJ, 2019[77]	Circulating C-reactive protein	1.000|OR≤0.75 or OR≥1.33	66,185 participants	European	3.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.95 (0.83-1.10)	0.527**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Plasma IL-6 receptor subunit alpha	1.000|OR≤0.75 or OR≥1.33	3,301 participants	European	60.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.98 (0.96-1.00)	0.035**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Insulin related markers															
Cornish AJ, 2019[77]	Fasting glucose	1.000|OR≤0.75 or OR≥1.33	96,496 participants	European	3.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.04 (0.92-1.18)	0.519**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Fasting proinsulin	1.000|OR≤0.75 or OR≥1.33	46,186 participants	European	6.1	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.97 (0.90-1.03)	0.310**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	HbA1C levels	0.999|OR≤0.75 or OR≥1.33	46,368 participants	European	1.8	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	1.02 (0.85-1.22)	0.866**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Plasma IGF–I	0.995|OR≤0.75 or OR≥1.33	3301 participants	European	1.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.88 (0.76-1.01)	0.064**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Other Biomarkers															
Zhang C, 2015[84]	Telomere length (GRS)	0.8|OR≥1.22	37,684 &9,190 & 2,240 participants	European	0.06-0.2 per SNP	5,100 cases and 4,831 controls	OR per 1000 base pair increase	European	Two-sample	IVW	1.25(0.92,1.69)	0.150	Stratified by age and sex; likelihood-based Mendelian randomization method; Alternative instrument selection strategy	No	Likely non-causal
Haycock PC, 2017[85]	Telomere length	1	9,190 participants	European	/	14,537 cases and 16,922 controls	OR per SD	European	Two-sample	Maximum likelihood	1.09(0.91,1.31)	0.340	Heterogeneity analysis, weighted median and MR-Egger	No	Likely non-causal
Protein& amino acid															

Au Yeung SL, 2019[86]	GDF-15	0.8|OR≥1.11 (R2=0.15) or OR≥1.10 (R2=0.21)	5,440 participants	European	15 or 21	4,562 cases and 382,756 controls	OR per SD	European	Two-sample	IVW (Fixed effect)	0.91(0.80,1.04)	/	Multiplicative random effect IVW; Lead SNP analysis; MR-Egger intercept test; Mendelian randomisation restricted to instruments from the same gene region (PGPEP1 or GDF15)	No	Unknown
Nimptsch K, 2017[87]	Adiponectin (ADIPOQ allele score)	0.8|OR≤0.61	2,880 participants	European and US	3	1,253 cases and 1,627 controls	OR per score unit	European and US	One-sample	Conditional logistic regression	0.97(0.91,1.04)	0.430	Restriction to Caucasians; Effect estimate in different study (HPFS and NHS); summary instrumental variable analysis using published data on genetic associations with adiponectin and colorectal cancer in a likelihood-based approach	No	Unknown
Nimptsch K, 2017[87]	Adiponectin (Incorporating the ADIPOQ allele score and plasma adiponectin concentrations)	0.8|OR≤0.76	2,880 participants	European and US	/	1,253 cases and 1,627 controls	OR per score unit	European and US	One-sample	Conditional logistic regression	0.73(0.40,1.34)	/	Restriction to Caucasians; Effect estimate in different study (HPFS and NHS)	No	Likely non-causal
Nimptsch K, 2015[88]	Fetuin-A (AHSG allele-score)	Limited power (not specified)	1,367 cases and 1,367 controls	Western European	21	1,367 cases and 1,367 controls	RR per 40mg/ml higher (aapprox 1 SD)	Western European	One-sample	Logistic regression	0.98(0.73,1.33)	/	Conditional logistic regression models additionally adjusted for matching factors and BMI	No	Unknown
Cornish AJ, 2019[77]	Blood carnitine	1.000|OR≤0.75 or OR≥1.33	7,824 participants	European	13.9	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.99 (0.92-1.06)	0.682**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Blood methionine	0.676|OR≤0.75 or OR≥1.33	7,824 participants	European	0.4	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.92 (0.70-1.19)	0.505**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Circulating adiponectin	1.000|OR≤0.75 or OR≥1.33	39,883 participants	European	1.8	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.93 (0.81-1.07)	0.309**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown
Cornish AJ, 2019[77]	Circulating fetuin-A	1.000|OR≤0.75 or OR≥1.33	9,055 & 2,119 participants	European, African American	14.3	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Wald ratio	0.98 (0.94-1.02)	0.370**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown

Cornish AJ, 2019[77]	Serum immunoglobulin E	0.997|OR≤0.75 or OR≥1.33	6,819 participants	European	1.6	26,397 cases and 41,481 controls	OR per SD	European	Two-sample	Maximum likelihood	0.92 (0.82-1.03)	0.159**	Weighted median, mode-based estimates, MR-Egger, leave-one-out analysis	No	Unknown

*: statistically significant threshold set up at P≤0.0001; **: statistically significant threshold set up at P≤0.0013, GI: genetic instrument, SNP: Single Nucleotide Polymorphism, OR: odds ratio, HR: hazard ratio, SD: standard deviation, GRS: genetic risk score, BMI: body mass index, IVW: inverse variance weighted, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, DPA: Docosapentaenoic acid, AA: arachidonic acid, DGLA: dihomo-γ-linolenic acid, LA: linoleic acid, ALA: α-Linolenic acid, HDL: high-density lipoprotein cholesterol, LD: linkage disequilibrium, LDL: low-density lipoprotein cholesterol, IL-6: interleukin 6, HbA1C: glycated hemoglobin, IGF-1: insulin-like growth factor 1, GDF-15: Growth differentiation factor 15.

Supplementary Table 6 Summary of overlapped meta-analyses of observational studies and Mendelian randomization studies

Biomarker	No. of overlapping studies	Agreement of Direction of Point Estimate	Agreement of Presence of Nominal Significance (p<0.05)	Reference
Overlapped results from meta-analyses of observational studies				
H. pylori infection	9	Y	N	6-12,20
HPV	8	Y	Y	13-19
Vitamin B9 [Folate]	6	N	N	35-38
Vitamin B12	5	N	N	36,38,39
Vitamin B6	5	Y	Y	36,41,42
Vitamin B2	2	Y	N	36,40
25-hydroxyvitamin D	10	Y	Y	45-51
CRP	3	Y	Y	23-25
IL-6	2	Y	NON	24,26
Fasting Glucose	6	Y	Y	27,28,30,31
C peptide	3	Y	Y	27-29
IGF 1	3	Y	Y	32,33
IGF 2	2	Y	Y	32,34
IGFBP 3	2	Y	NON	32,89
Triglycerides	3	Y	N	2,3
HDL–cholesterol	2	Y	Y	2,3
Adiponectin	7	N	N	59-63,90
Leptin	4	Y	N	62,66,90
Homocysteine	3	Y	Y	36,38
Telomere Length	3	Y	N	57,58
Overlapped results from Mendelian randomisation studies				
25-hydroxyvitamin D	8	N	NON	72-77
Adiponectin	3	Y	NON	77,87,91
Fetuin-A	2	Y	NON	77,88
DHA 22:6n-3	2	Y	NON	78,79
DPA 20:5n-3	2	Y	NON	78,79
EPA 20:5n-3	2	N	NON	78,79
AA 20:4n-6	2	Y	Y	78,79
LA 18:2n-6	2	Y	Y	78,79
Triglyceride	3	N	NON	77,80,81
LDL–cholesterol	3	Y	NON	80,81
HDL–cholesterol	3	N	NON	80,81
Total cholesterol	2	Y	N	77,80
C-reactive protein	3	N	N	82,83
Telomere length	2	Y	NON	84,85
Comparison between the largest meta-analyses of observational studies and the largest Mendelian randomisation studies				
25-hydroxyvitamin D	/	Y	N	49,72
Selenium	/	Y	NON	44,77
Vitamin B12	/	N	N	36,77
Vitamin B6	/	N	N	41,77
Vitamin E	/	Y	NON	53,77
Zinc	/	N	NON	54,77
DHA 22:6n-3	/	N	N	1,78
EPA 20:5n-3	/	N	N	1,78
DPA 20:5n-3	/	N	NON	1,78
Total cholesterol	/	Y	NON	3,80
Triglyceride	/	N	NON	3,80
LDL–cholesterol	/	Y	NON	3,80
HDL–cholesterol	/	N	NON	3,80
C-reactive protein	/	Y	N	24,83
IL-6	/	N	NON	24,77
Fasting glucose	/	Y	N	27,77
HbA1C	/	Y	NON	27,77
IGF–I	/	N	N	32,77
Adiponectin	/	Y	N	59,77
Telomere length	/	Y	NON	58,85

Y: agree, N: disagree, NON: non-significant association has been identified, CRC: colorectal cancer, H. pylori: helicobacter pylori, HPV: human papillomavirus infection, CRP: C-reactive protein, IL-6: Interleukin 6, IGF 1/2: Insulin-like growth factor 1/2, IGFBP 3: Insulin-like growth factor-binding protein 3, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, DHA: Docosahexaenoic acid, DPA: Docosapentaenoic acid, EPA: Eicosapentaenoic acid, AA: arachidonic acid, LA: linoleic acid, HbA1c: glycated hemoglobin

Supplementary Table 7 Characteristics and main findings of meta-analyses of observational studies reporting unique non-genetic biomarkers and CRC risk (DL, PM, HKSJ estimators)

Author/Year	Biomarker	No of studies	No of cases	No of participants	Metric	Effect size, DL (95%CI)	P, DL	I^2, DL	P_{Egger}, DL	95%PI, DL	Effect size, PM (95%CI)
Fatty acid/Lipid metabolism biomarkers											
Yang B,2014	LC n-3 PUFA	3	421	1,826	RR	0.58(0.40,0.84)	0.0042	0.00%	0.78	0.58(0.40,0.84)	0.58(0.40,0.84)
Yang B,2014	Biospecimen EPA 20:5 (n-3)	4	421	1,826	RR	0.64(0.43,0.94)	0.0242	0.00%	0.48	0.64(0.43,0.94)	0.64(0.43,0.94)
Yang B,2014	Biospecimen DHA 22:6 (n-3)	4	421	1,826	RR	0.53(0.32,0.87)	0.0124	27.00%	0.12	0.53(0.32,0.87)	0.53(0.32,0.88)
Yang B,2014	Biospecimen DPA 22:5 (n-3)	3	243	1,366	RR	0.57(0.33,0.98)	0.0433	15.54%	0.44	0.57(0.33,0.98)	0.57(0.32,0.99)
Yang B,2014	Blood EPA 20:5 (n-3)	5	195	384	SMD	-0.76(-1.55,0.03)	0.0603	93.24%	0.00	-0.76(-1.56,0.03)	-0.99(-2.89,0.92)
Yang B,2014	Blood DHA 22:6 (n-3)	5	195	384	SMD	-0.09(-0.27,0.09)	0.3098	0.00%	0.31	-0.09(-0.27,0.09)	-0.10(-0.27,0.09)
Yang B,2014	Blood DPA 22:5 (n-3)	5	195	384	SMD	0.36(-0.10,0.83)	0.1245	81.83%	0.00	0.36(-0.10,0.83)	0.43(-0.27,1.12)
Yang B,2014	Adipose EPA 20:5 (n-3)	2	93	204	SMD	0.07(-0.20,0.35)	0.6024	0.00%	/	0.07(-0.20,0.35)	0.08(-0.20,0.35)
Yang B,2014	Adipose DHA 22:6 (n-3)	2	93	204	SMD	-0.02(-0.35,0.30)	0.892	26.74%	/	-0.02(-0.35,0.30)	-0.02(-0.35,0.30)
Yang B,2014	Adipose DPA 22:5 (n-3)	2	93	204	SMD	0.12(-0.16,0.39)	0.4081	0.00%	/	0.12(-0.16,0.39)	0.12(-0.16,0.39)
Yao X,2015	HDL	12	2,542	136,698	RR	0.84(0.69,1.02)	0.0768	42.55%	0.39	0.84(0.69,1.02)	0.84(0.69,1.02)
Yao X,2015	LDL	5	1,626	9,175	RR	1.04(0.60,1.81)	0.8906	82.66%	0.13	1.04(0.60,1.81)	1.04(0.57,1.92)
Yao X,2015	Total cholesterol	28	10,892	7,725,310	RR	1.11(1.01,1.21)	0.0294	46.75%	0.54	1.11(1.01,1.21)	1.11(0.99,1.24)
Yao X,2015	Triglyceride	19	8,127	2,252,217	RR	1.18(1.04, 1.34)	0.012	47.77%	0.20	1.18(1.04,1.33)	1.17(1.02,1.35)
Infectious agents											
Ibragimova MK,2018	HPV	17	1,722	2,468	RR	2.69(1.86,3.90)	1.61E-07	25.50%	0.10	2.70(1.86,3.90)	2.93(1.87,4.57)
Bai B,2016	Human cytomegalovirus infection	4	480	960	OR	6.47(4.40,9.52)	2.91E-21	0.00%	0.73	6.47(4.40,9.52)	6.47(4.40,9.52)
Boleij A,2011	Streptococcus bovis	6	189	340	OR	9.68(4.99,18.81)	2.03E-11	0.00%	0.51	9.68(4.99,18.81)	9.68(4.99,18.81)
Liu C,2016	H.pylori	20	3,228	4,377	OR	1.37(1.10,1.71)	0.0048	61.09%	0.78	1.37(1.10,1.71)	1.38(1.04,1.84)
Repass J,2018	F. nucleatum	2	139	278	r	0.40(0.17,0.62)	0.0005	34.95%	/	0.38(0.17,0.55)	0.40(0.17,0.62)
Liu H,2016	Enterobacteriaceae	2	37	76	SMD	2.62(0.55,4.69)	0.0133	88.74%	/	2.62(0.55,4.69)	2.62(0.55,4.69)

Liu H,2016	Bifidobacterium	4	127	315	SMD	-3.24(-6.47, -0.02)	0.0486	98.25%	0.06	-3.24(-6.47, -0.02)	-3.24(-6.33, -0.15)
Liu H,2016	Faecalibacterium prausnitzii	3	86	233	SMD	-0.32(-0.59, -0.05)	0.0192	0.00%	0.63	-0.32(-0.59, -0.05)	-0.32(-0.59, -0.05)
Liu H,2016	Total bacteria	3	86	233	SMD	0.21(-0.53,0.96)	0.5758	75.81%	0.05	0.21(-0.53,0.96)	0.29(-0.75,1.32)
Krishnan S,2014	Streptococcus bovis in faeces	3	148	414	OR	2.84(0.48,16.74)	0.2483	66.82%	0.18	2.84(0.48,16.74)	3.10(0.68,14.20)
Liu H,2016	Lactobacillus	4	127	315	SMD	-1.78(-3.76, 0.20)	0.0787	97.31%	0.03	-1.78(-3.76,0.20)	-1.85(-5.35,1.66)
Liu H,2016	Bacteroides-Prevotella group	3	97	255	SMD	-0.70(-2.53,1.14)	0.4552	96.27%	0.84	-0.70(-2.53,1.14)	-0.70(-2.35,0.95)
Liu H,2016	Escherichia coli	2	90	239	SMD	1.38(-1.36,4.12)	0.3239	98.00%	/	1.38(-1.36,4.12)	1.38(-1.36,4.12)
Inflammatory Markers											
Zhou B,2014	CRP	18	4,779	152,942	RR	1.12(1.05,1.21)	0.0013	51.74%	0.02	1.12(1.05,1.20)	1.13(1.04,1.23)
Zhou B,2014	IL-6	6	1,125	9,909	RR	1.10(0.88,1.36)	0.4012	34.82%	0.11	1.10(0.88,1.36)	1.10(0.88,1.36)
Insulin related biomarkers											
Xu J,2016	Fasting glucose	26	20,390	5,105,567	RR	1.23(1.11,1.36)	8.92E-05	40.90%	0.00	1.23(1.11,1.36)	1.23(1.11,1.36)
Xu J,2016	HOMA-IR	9	2,956	18,358	RR	1.54(1.23,1.92)	0.0001	30.60%	0.12	1.54(1.23,1.92)	1.52(1.24,1.86)
Xu J,2016	Fasting insulin	11	3,191	26,301	OR	1.15(1.19,1.69)	1.28E-04	0.00%	0.70	1.42(1.19,1.69)	1.42(1.19,1.69)
Chi F,2013	IGF 1	17	3,807	11,613	OR	1.28(1.07,1.53)	0.0061	20.62%	0.17	1.28(1.07,1.53)	1.28(1.07,1.54)
Chi F,2013	IGF 2	6	783	4,007	OR	1.52(1.09,2.11)	0.0134	14.94%	0.64	1.52(1.09,2.11)	1.52(1.08,2.12)
Chi F,2013	IGFBP 1	7	2,154	6,439	OR	0.85(0.69,1.04)	0.1043	3.68%	0.26	0.85(0.69,1.04)	0.84(0.69,1.04)
Chi F,2013	IGFBP 2	3	1,348	2,962	OR	0.77(0.41,1.43)	0.4006	68.21%	0.01	0.77(0.41,1.43)	0.77(0.41,1.43)
Chi F,2013	IGFBP 3	16	3,755	11,509	OR	0.88(0.71,1.10)	0.2680	45.74%	0.31	0.88(0.71,1.10)	0.88(0.69,1.11)
Xu J,2016	HbA1c	8	2,137	45,569	RR	1.23(0.98,1.54)	0.0719	24.77%	0.31	1.23(0.98,1.54)	1.23(0.97,1.55)
Xu J,2016	C-peptide	11	3,211	13,888	RR	1.32(1.02,1.70)	0.0325	48.09%	0.50	1.32(1.02,1.70)	1.34(0.99,1.79)
Micronutrients											
Ma YL,2011	25-hydroxyvitamin D	10	3,142	7,840	RR	0.68(0.57,0.81)	2.87E-05	0.00%	0.61	0.68(0.57,0.82)	0.68(0.57,0.81)
Lee JE,2011	1,25-dihydroxyvitamin D	4	625	1,801	OR	1.02(0.66,1.56)	0.9357	39.13%	0.63	1.02(0.66,1.56)	1.01(0.67,1.53)
Ben S, 2018	Vitamin B2	2	1,593	32,962	RR	0.73(0.59,0.92)	0.0069	0.00%	/	0.74(0.59,0.92)	0.73(0.59,0.92)
Larsson SC,2010	Vitamin B6	4	883	2,207	RR	0.52(0.38,0.71)	4.39E-05	0.00%	0.97	0.52(0.38,0.71)	0.52(0.38,0.71)
S. Shiao SPK,2018	Vitamin B12	8	3,296	8,290	SMD	-0.07(-0.13, -0.003)	0.0378	52.44%	0.00	-0.07(-0.19,0.05)	-0.05(-0.12,-0.002)

Zhang D, 2015	Folate	12	1,159	2,982	SMD	-1.01(-1.52, -0.51)	7.66E-05	98.01%	0.00	-1.01(-1.93, -0.10)	-1.29(-2.27, -0.31)
Dong YH,2017	Vitamin E	9	310	5,927	SMD	-0.74(-1.30, -0.17)	0.0108	92.33%	0.00	-0.74(-1.31, -0.17)	-0.79(-1.63,0.05)
Vinceti M,2018	Selenium	8	2,627	712,746	OR	0.86(0.70,1.06)	0.1585	0.00%	0.84	0.86(0.70,1.06)	0.86(0.70,1.06)
Gumulec J,2014	Serum Zinc	5	313	529	SMD	0.05(-2.55,2.64)	0.9725	98.98%	0.66	0.05(-2.55,2.64)	0.05(-3.47,3.56)
Gumulec J,2014	Tissue Zinc	10	234	398	SMD	-0.24(-1.50,1.02)	0.7088	95.34%	0.00	-0.24(-1.50,1.02)	-0.70(-2.84,1.45)
Other Biomarkers											
Zhang BL,2015	Blood group O	8	6,931	3,219,151	OR	0.90(0.86,0.95)	5.78E-05	0.00%	0.22	0.90(0.86,0.95)	0.90(0.86,0.95)
Zhang BL,2015	Blood group AB	8	6,931	3,191,289	OR	0.97(0.86,1.10)	0.6443	0.00%	0.41	0.97(0.86,1.10)	0.97(0.86,1.10)
Zhang BL,2015	Blood group A	8	6,931	3,214,941	OR	1.03(0.96,1.12)	0.3794	43.35%	0.07	1.04(0.96,1.12)	1.02(0.92,1.13)
Zhang BL,2015	Blood group B	8	6,931	3,193,532	OR	1.01(0.93,1.09)	0.8975	0.00%	0.40	1.01(0.93,1.09)	1.01(0.93,1.09)
Naing C,2017	Telomere Length	8	951	2,569	OR	1.01(0.77,1.34)	0.9270	30.40%	0.24	1.01(0.77,1.34)	1.01(0.77,1.34)
Jiang R,2016	Enterolactone	3	762	2,408	RR	1.11(0.93, 1.32)	0.2668	44.60%	0.06	1.11(0.93,1.32)	1.12(0.92,1.36)
Protein& amino acids											
Lu S,2017	Total Adiponectin	8	3,420	8,937	RR	0.79(0.68,0.92)	0.0024	5.37%	0.35	0.79(0.68,0.92)	0.79(0.68,0.92)
Yang G,2016	Resistin	11	965	2,290	SMD	0.65(0.24,1.05)	0.0016	93.12%	0.94	0.65(0.24,1.05)	0.65(0.19,1.10)
Shiao SPK,2018	Homocysteine	8	4,047	9,604	SMD	0.13(0.03, 0.22)	0.0072	74.80%	0.73	0.13(-0.04,0.29)	0.12(0.05,0.20)
Yu DH,2018	Angiogenin	2	188	240	SMD	1.53(0.49,2.58)	0.0043	88.33%	/	1.53(0.48,2.58)	1.53(0.48,2.58)
Xing XJ,2014	MMP7	10	625	1,020	SMD	2.15(1.46,2.84)	9.65E-10	94.65%	0.00	2.15(0.90,3.40)	2.31(0.90,3.72)
Li XX,2014	TLR-4 protein	3	168	283	OR	4.75(1.16,19.37)	0.0300	77.43%	0.00	4.75(1.16,19.37)	4.76(1.14,19.83)
Sun SJ,2016	HER‑2(human epidermal growth factor receptor 2) expression	13	932	1,453	OR	10.43(5.48,19.89)	8.77E-11	63.02%	0.00	10.43(5.48,19.88)	11.33(5.44,23.59)
Feng Z, 2015	Ferritin	7	277	927	SMD	-1.56(-2.70, -0.41)	0.0079	97.47%	0.00	-1.56(-2.70, -0.41)	-1.57(-3.06, -0.08)
Ouyang Z,2017	CD26	9	952	1,809	SMD	-0.33(-2.97,2.30)	0.8033	99.63%	0.27	-0.34(-5.11,4.44)	
Gialamas SP,2013	Leptin	23	3,508	7,478	SMD	0.18(-0.04,0.40)	0.1094	94.01%	0.41	0.18(-0.22,0.58)	0.20(-0.32,0.72)

CRC: colorectal cancer, HKSJ: Hartung-Knapp-Sidik-Jonkman, 1PEgger: The P value for small study effect test, 2Psig: The P value for excess significance test, RR: risk ratio, SMD: standard mean difference, OR: odds ratio, r: standardized correlation coefficient, LC n-3 PUFA: long chain n-3 polyunsaturated fatty acid, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, DPA: Docosapentaenoic acid, HDL: high-density

lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, HPV: Human papillomavirus, CRP: C-reactive protein, IL-6: Interleukin 6, HOMA-IR: homeostatic model assessment-insulin resistance, IGF 1/2: Insulin-like growth factor 1/2, IGFBP 1/2/3: Insulin-like growth factor-binding protein 1/2/3, HbA1c: glycated hemoglobin, MMP7: matrix metalloproteinase-7, CD26: dipeptidyl peptidase IV.

Supplementary Table 7 (Continued)

Biomarker	P, PM	I^2, PM	P_{Egger}, PM	95%PI, PM	Effect size, HKSJ (95%CI)	P, HKSJ	I^2, HKSJ	P_{Egger}, HKSJ	95%PI, HKSJ
Fatty acid/Lipid metabolism biomarkers									
LC n-3 PUFA	0.0042	0.00%	0.78	0.58(0.40,0.84)	0.58(0.40,0.84)	0.0042	0.21%	0.78	0.58(0.40,0.84)
Biospecimen EPA 20:5 (n-3)	0.0242	0.00%	0.48	0.64(0.43,0.94)	0.64(0.42,0.96)	0.0314	9.24%	0.50	0.64(0.42,0.96)
Biospecimen DHA 22:6 (n-3)	0.0142	30.68%	0.12	0.53(0.32,0.88)	0.51(0.28,0.93)	0.0266	46.59%	0.19	0.51(0.28,0.93)
Biospecimen DPA 22:5 (n-3)	0.0458	17.69%	0.44	0.57(0.33,0.99)	0.56(0.29,1.07)	0.0788	37.89%	0.46	0.56(0.30,1.07)
Blood EPA 20:5 (n-3)	0.3104	98.89%	0.01	-0.98(-2.89,0.92)	-0.98(-2.87,0.91)	0.3080	98.87%	0.01	-0.98(-2.87,0.91)
Blood DHA 22:6 (n-3)	0.3098	0.00%	0.31	-0.09(-0.27,0.09)	-0.07(-0.31,0.17)	0.5718	35.10%	0.41	-0.07(-0.31,0.17)
Blood DPA 22:5 (n-3)	0.2293	92.11%	0.00	0.43(-0.27,1.12)	0.43(-0.27,1.12)	0.2292	92.11%	0.00	0.43(-0.27,1.12)
Adipose EPA 20:5 (n-3)	0.6024	0.00%	/	0.07(-0.20,0.35)	0.07(-0.21,0.36)	0.6083	3.39%	/	0.07(-0.21,0.36)
Adipose DHA 22:6 (n-3)	0.8920	26.74%	/	-0.02(-0.35,0.30)	-0.02(-0.37,0.32)	0.8999	35.64%	/	-0.02(-0.37,0.32)
Adipose DPA 22:5 (n-3)	0.4081	0.00%	/	0.12(-0.16,0.39)	0.12(-0.16,0.39)	0.4082	0.07%	/	0.12(-0.16,0.40)
HDL	0.0727	40.66%	0.40	0.84(0.69,1.02)	0.83(0.67,1.04)	0.1043	53.08%	0.39	0.83(0.67,1.04)
LDL	0.8909	85.73%	0.15	1.04(0.57,1.92)	1.04(0.57,1.92)	0.8908	85.67%	0.16	1.04(0.57,1.92)
Total cholesterol	0.0688	66.89%	0.57	1.11(0.99,1.25)	1.11(0.98,1.27)	0.1043	76.10%	0.60	1.12(0.98,1.27)
Triglyceride	0.0239	55.92%	0.20	1.17(1.02,1.35)	1.17(0.99,1.36)	0.0598	47.77%	0.22	1.17(0.99,1.37)
Infectious agents									
HPV	2.41E-06	41.28%	0.15	2.93(1.87,4.57)	3.52(1.77,7.00)	0.0003	75.66%	0.6453	3.52(1.77,7.00)
Human cytomegalovirus infection	2.91E-21	0.00%	0.73	6.47(4.40,9.52)	6.47(4.23,9.89)	6.78E-18	13.74%	0.70	6.47(4.23,9.89)
Streptococcus bovis	2.03E-11	0.00%	0.51	9.68(4.99,18.81)	9.44(4.43,20.11)	5.95E-09	18.72%	0.57	9.44(4.43,20.11)
H.pylori	0.0277	78.87%	0.88	1.38(1.04,1.84)	1.38(1.01,1.89)	4.00E-02	82.00%	0.90	1.38(1.02,1.89)

F. nucleatum	0.0005	34.95%	/	0.38(0.17,0.55)	0.40(0.16,0.63)	0.0010	40.05%	/	0.38(0.16,0.56)
Enterobacteriaceae	0.0133	88.74%	/	2.62(0.55,4.69)	2.62(0.62,4.61)	0.0101	87.87%	/	2.62(0.62,4.61)
Bifidobacterium	0.0397	98.09%	0.07	-3.24(-6.33, -0.15)	-3.24(-6.32, -0.16)	0.0390	98.08%	0.07	-3.24(-6.32,-0.16)
Faecalibacterium prausnitzii	0.0192	0.00%	0.63	-0.32(-0.59,-0.05)	-0.31(-0.69,0.06)	0.1000	25.76%	0.60	-0.31(-0.69,0.06)
Total bacteria	0.5842	87.64%	0.05	0.29(-0.75,1.32)	0.29(-0.74,1.31)	0.5825	87.31%	0.07	0.29(-0.74,1.31)
Streptococcus bovis in faeces	0.1457	56.38%	0.18	3.10(0.68,14.20)	3.10(0.68,14.20)	0.1456	56.37%	0.23	3.10(0.68,14.20)
Lactobacillus	0.3014	99.15%	0.19	-1.85(-5.35,1.66)	-1.85(-5.33,1.64)	0.2993	99.15%	0.19	-1.85(-5.33,1.64)
Bacteroides-Prevotella group	0.4072	95.38%	0.84	-0.70(-2.35,0.95)	-0.70(-2.33,0.94)	0.4030	95.30%	0.83	-0.70(-2.33,0.94)
Escherichia coli	0.3239	98.00%	/	1.38(-1.36,4.12)	1.38(-1.34,4.10)	0.3195	97.96%	/	1.38(-1.34,4.10)
Inflammatory Markers									
CRP	0.0031	65.11%	0.03	1.13(1.04,1.23)	1.14(1.04,1.25)	0.0059	72.80%	0.05	1.14(1.04,1.25)
IL-6	0.4029	35.06%	0.11	1.10(0.88,1.36)	1.09(0.85,1.39)	0.4959	47.99%	0.19	1.09(0.85,1.39)
Insulin related biomarkers									
Fasting glucose	9.60E-05	42.10%	0.00	1.23(1.11,1.36)	1.27(1.11,1.45)	0.0006	66.17%	0.0106	1.27(1.11,1.45)
HOMA-IR	5.76E-05	20.89%	0.10	1.52(1.24,1.86)	1.56(1.22,1.98)	0.0003	38.91%	0.18	1.56(1.22,1.98)
Fasting insulin	1.28E-04	0.00%	0.70	1.42(1.19,1.69)	1.40(1.12,1.74)	0.0031	24.65%	0.86	1.40(1.12,1.74)
IGF 1	0.0069	23.68%	0.18	1.28(1.07,1.54)	1.31(1.05,1.63)	0.0187	48.42%	0.28	1.31(1.05,1.63)
IGF 2	0.0153	16.80%	0.65	1.52(1.08,2.12)	1.52(0.99,2.34)	0.0549	42.30%	0.62	1.52(0.99,2.34)
IGFBP 1	0.1056	4.90%	0.26	0.84(0.69,1.04)	0.81(0.61,1.08)	0.1585	43.13%	0.42	0.81(0.61,1.09)
IGFBP 2	0.4008	68.29%	0.01	0.77(0.41,1.43)	0.76(0.41,1.43)	0.4016	68.77%	0.02	0.77(0.41,1.43)
IGFBP 3	0.2844	51.93%	0.32	0.88(0.69,1.11)	0.88(0.70,1.10)	0.2680	45.74%	0.31	0.88 0.71 1.10
HbA1c	0.0814	89.56%	0.31	1.23(0.97,1.56)	1.25(0.93,1.67)	0.1414	53.83%	0.30	1.25(0.93,1.67)
C-peptide	0.0514	60.90%	0.63	1.34(0.99,1.79)	1.35(0.97,1.89)	0.0788	70.63%	0.73	1.35(0.97,1.89)
Micronutrients									
25-hydroxyvitamin D	2.87E-05	0.00%	0.61	0.68(0.57,0.82)	0.67(0.54,0.83)	0.0002	20.49%	0.79	0.67(0.54,0.83)
1,25-dihydroxyvitamin D	0.9443	34.36%	0.64	1.02(0.67,1.53)	1.02(0.66,1.59)	0.9302	42.59%	0.64	1.02(0.66,1.59)
Vitamin B2	0.0069	0.00%	/	0.74(0.59,0.92)	0.74(0.57,0.95)	0.0200	9.32%	/	0.74(0.58,0.95)

Vitamin B6	4.75E-05	0.00%	0.97	0.52(0.38,0.71)	0.52(0.38,0.71)	0.0012	0.89%	0.97	0.52(0.38,0.72)
Vitamin B12	0.0397	39.77%	0.00	-0.06(-0.16,0.04)	-0.07(-0.14, -0.003)	0.0384	54.91%	0.03	-0.07(-0.19,0.05)
Folate	0.0097	99.56%	0.04	-1.29(-3.06,0.48)	-1.29(-2.29, -0.30)	0.0105	99.57%	0.04	-1.29(-3.09,0.51)
Vitamin E	0.0650	96.62%	0.01	-0.79(-1.63,0.05)	-0.79(-1.63,0.05)	0.0650	96.61%	0.01	-0.79(-1.63,0.05)
Selenium	0.1585	0.00%	0.84	0.86(0.70,1.06)	0.86(0.62,1.18)	0.3509	42.92%	0.7895	0.86(0.62,1.18)
Serum Zinc	0.9788	99.44%	0.73	0.05(-3.47,3.56)	0.05(-3.47,3.56)	0.9788	99.40%	0.73	0.05(-3.47,3.56)
Tissue Zinc	0.5236	98.52%	0.00	-0.70(-2.84,1.45)	-0.76(-3.08,1.55)	0.5187	98.75%	0.00	-0.76(-3.08,1.55)
Other Biomarkers									
Blood group O	5.78E-05	0.00%	0.22	0.90(0.86,0.95)	0.91(0.84,0.99)	0.0445	54.58%	0.23	0.91(0.84,0.99)
Blood group AB	0.6443	0.00%	0.41	0.97(0.86,1.10)	0.94(0.73,1.21)	0.6416	61.18%	0.44	0.94(0.73,1.21)
Blood group A	0.6917	65.94%	0.08	1.02(0.92,1.13)	1.01(0.90,1.14)	0.8533	75.87%	0.12	1.01(0.90,1.14)
Blood group B	0.8975	0.00%	0.40	1.01(0.93,1.09)	1.00(0.91,1.10)	0.9963	18.12%	0.41	1.00(0.91,1.10)
Telomere Length	0.9272	30.34%	0.26	1.01(0.77,1.34)	1.02(0.75,1.40)	0.8842	42.82%	0.34	1.02(0.75,1.40)
Enterolactone	0.2710	51.36%	0.06	1.12(0.92,1.36)	1.14(0.89,1.47)	0.2924	66.71%	0.06	1.14(0.89,1.47)
Protein& amino acids									
Total Adiponectin	0.0025	6.14%	0.35	0.79(0.68,0.92)	0.78(0.65,0.95)	0.0143	39.81%	0.38	0.79(0.65,0.95)
Resistin	0.0059	94.79%	0.94	0.65(0.19,1.11)	0.65(0.19,1.11)	0.0059	94.79%	0.94	0.65(0.19,1.11)
Homocysteine	2.10E-03	65.62%	0.68	0.13(-0.02, 0.27)	0.13(0.04,0.21)	0.0030	68.35%	0.69	0.13(-0.03,0.28)
Angiogenin	0.0043	88.33%	/	1.53(0.48,2.58)	1.53(0.52,2.54)	0.0030	87.41%	/	1.53(0.52,2.54)
MMP7	0.0013	98.80%	0.00	2.31(-0.24, 4.86)	2.31(0.91,3.71)	0.0013	98.80%	0.00	2.31(-0.24,4.86)
TLR-4 protein	0.0320	78.07%	0.00	4.76(1.14, 19.83)	4.75(1.16,19.45)	0.0304	77.55%	0.01	4.75(1.16,19.46)
HER‑2(human epidermal growth factor receptor 2) expression	8.77E-11	71.76%	0.00	11.33(5.44,23.59)	11.82(5.36,26.08)	9.33E-10	63.02%	0.00	11.82(5.36,26.08)
Ferritin	0.0391	98.51%	0.00	-1.57(-3.06, -0.08)	-1.57(-3.06, -0.08)	0.0388	98.50%	0.00	-1.57(-3.06, -0.08)
CD26	/	/	/	/	-0.33(-4.35,3.70)	0.8737	99.84%	0.45	-0.33(-7.62,6.97)
Leptin	0.4544	99.03%	0.58	0.20(-0.75,1.14)	0.20(-0.32,0.72)	0.4551	99.03%	0.58	0.20(-0.75,1.14)

Supplementary Table 8 Meta-analyses of RCTs on supplementary micronutrients and CRC risk													
First author, year	Ethicity	Population	Biomarker proxies	Dose	Comparison	Duration	No of studies	No of event	No of participants	Metric	Model	Effect size (95%CI)	I2(%)
Arain MA,2010[92]	/	Healthy people aged over 40 years old	Vitamin E	50mg/day; 400IU/day; 600IU/second day	Placebo	7-10 years	4	574	94,069	RR	Fixed	0.89(0.76,1.05)	7%
Bjelakovic G,2014[93]	/	Healthy people or with low-trauma, osteoporotic or fractureisolated systolic hypertension aged over 50 years old	Vitamin D3 (Cholecalciferol)	800IU/day; 800 IU plus calcium 1000 mg daily; 400 IU plus calcium 1000 mg daily; 1000IU/day plus calcium 1400 to 1500 mg daily; 100,000 IU/4 months; 100,000 IU oral vitamin D/3-monthly	Placebo or no intervention	1-7 years	5	436	45,598	RR	Random	1.11(0.92,1.34)	0%
Bristow SM,2013[94]	/	Healthy people aged over 40 years old	Calcium	>500 mg/d	Placebo	2-5 years	8	83	9,863	RR	Random	1.38(0.89,2.15)	0%
Druesne-Pecollo N,2010[95]	/	Smokers or asbestos workers, or not	Beta-carotene given singly or in combination with other antioxidants	6–15 mg/day or 20–30 mg/day	Placebo	4-25 years	7	957	151,118	HR	Fixed	0.96 (0.85,1.09)	/
Qin T,2015[96]	Mixed	Vascular disease, diabetes, colorectal adenoma patients or healthy people aged over 57 years old	Folic acid	0.5-2.5mg/day	Placebo	27-88 months	8	381	34,598	RR	Fixed	1.00(0.82,1.22)	0%
Qin X,2013[97]	Mixed	Vascular disease, diabetes, colorectal adenoma patients or healthy people aged over 57 years old	Folic acid	0.5-2.5mg/day	Placebo	36-88 months	7	377	33,824	RR	Random	1.01(0.82,1.23)	/
RR: risk ratio; HR: hazard ratio													

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